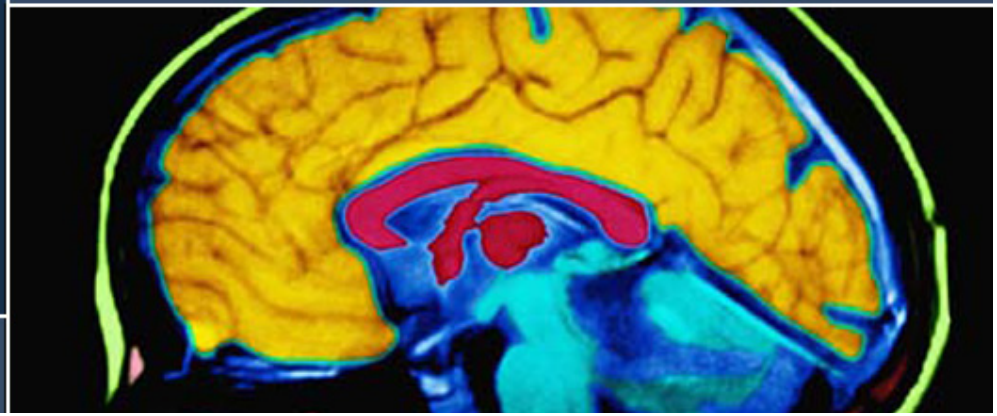
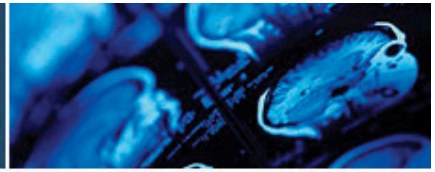
National Institute of Neurological Disorders and Stroke

Office of Translational Research: An Overview

TRIG
May 2nd, 2013

Rajesh Ranganathan, PhD
Director, Office of Translational Research
NINDS
rajesh.ranganathan@nih.gov





Outline

- The Changing Landscape of Neuroscience Therapeutic Development
- NINDS Office of Translational Research (OTR)
  - Anticonvulsant Screening Program (ASP)
  - Cooperative Agreement Program (CAP)
  - SMA Project
  - Blueprint Neurotherapeutics (BPN)
  - Small Business Program (SBIR)
  - CounterACT
- Discussion

Outline

- NINDS Office of Translational Research (OTR)
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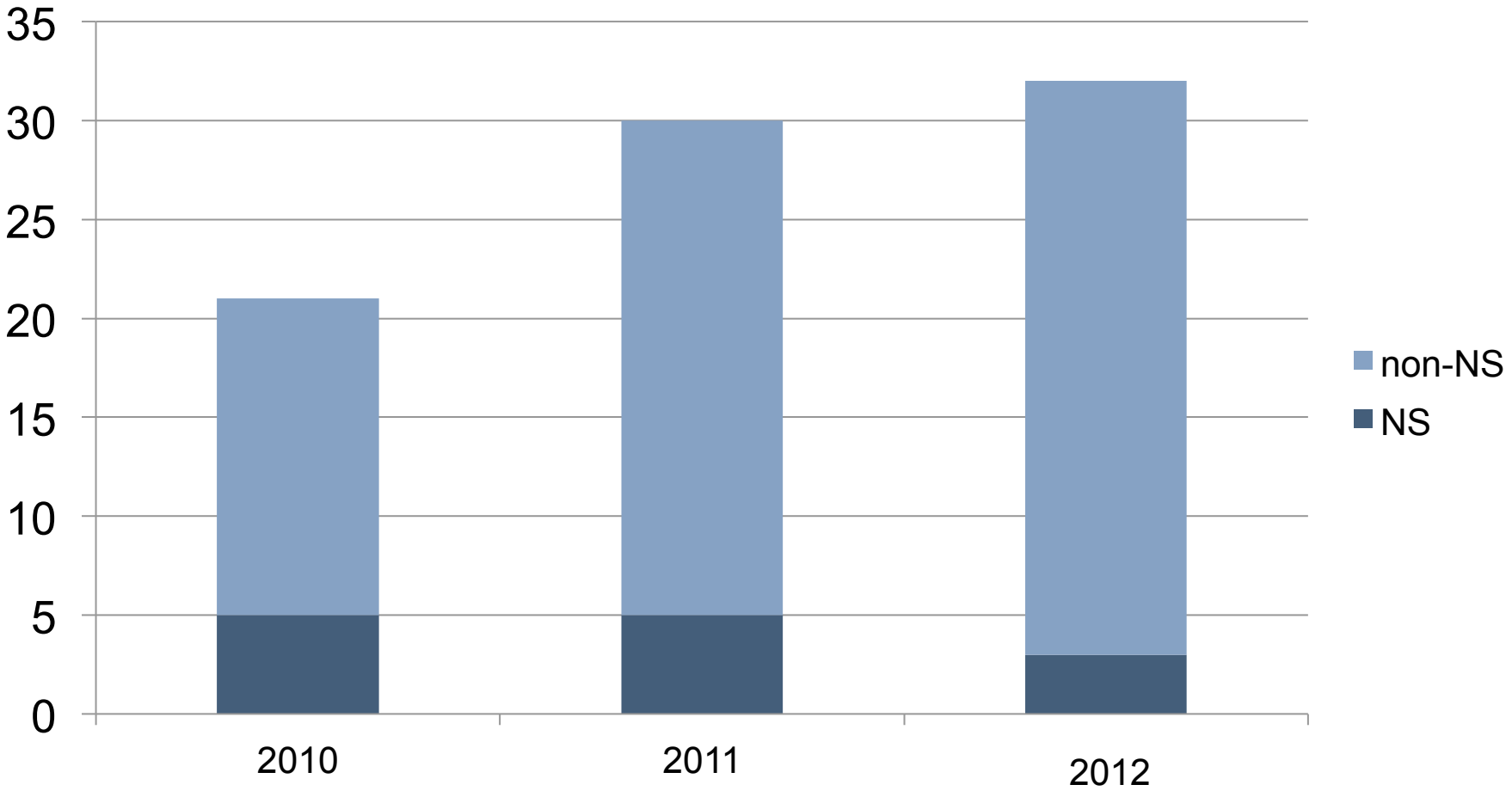
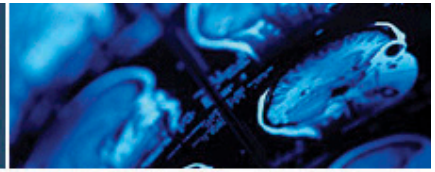
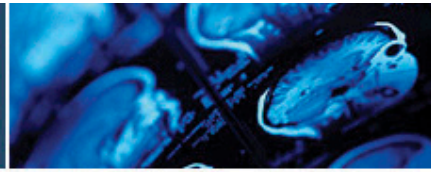
FDA Drug Approvals





Neurotherapeutics FDA Approvals

Brand Names	Drug Name	Company	Indication
2010			
Ampyra	dalfampredine	Acorda Therapeutics	MS
Pradaxa	dabigatran etexilate	Boehringer Ingelheim	stroke
Gilenya	fingolimod	Novartis	MS
Botox	onabotulinumtoxinA	Allergan Inc	dystonia, migraine (2 approvals)
2011			
Potiga	ezogabine	Valeant Pharmaceuticals	seizure
Onfi	clobazam	Lundbeck	seizure
Horizant	gabapentin enacarbil	GlaxoSmithKline, XenoPort	restless leg syndrome
DaTSCAN	loflupane I-123	GE Healthcare	PD imaging agent (SPECT)
Gadavist	gadobtrol	Bayer HealthCare	AD imaging agent (MRI)
2012			
Aubagio	teriflunomide	Sanofi Aventis	MS
Amyvid	Florbetapir F 18	Avid Radiopha	AD imaging agent (PET)
Afinitor Disperz	everolimus (new formulation of existing drug)	Novartis	subependymal giant cell astrocytoma (a brain tumor)



Industry is leaving NS R&D

R&D Cuts Curb Brain-Drug Pipeline

Development of new medicines for brain disorders could be threatened as major drug makers scale back research THE WALL STREET JOURNAL. March 27, 2011

Novartis to shut brain research facility

Nature, December 2011

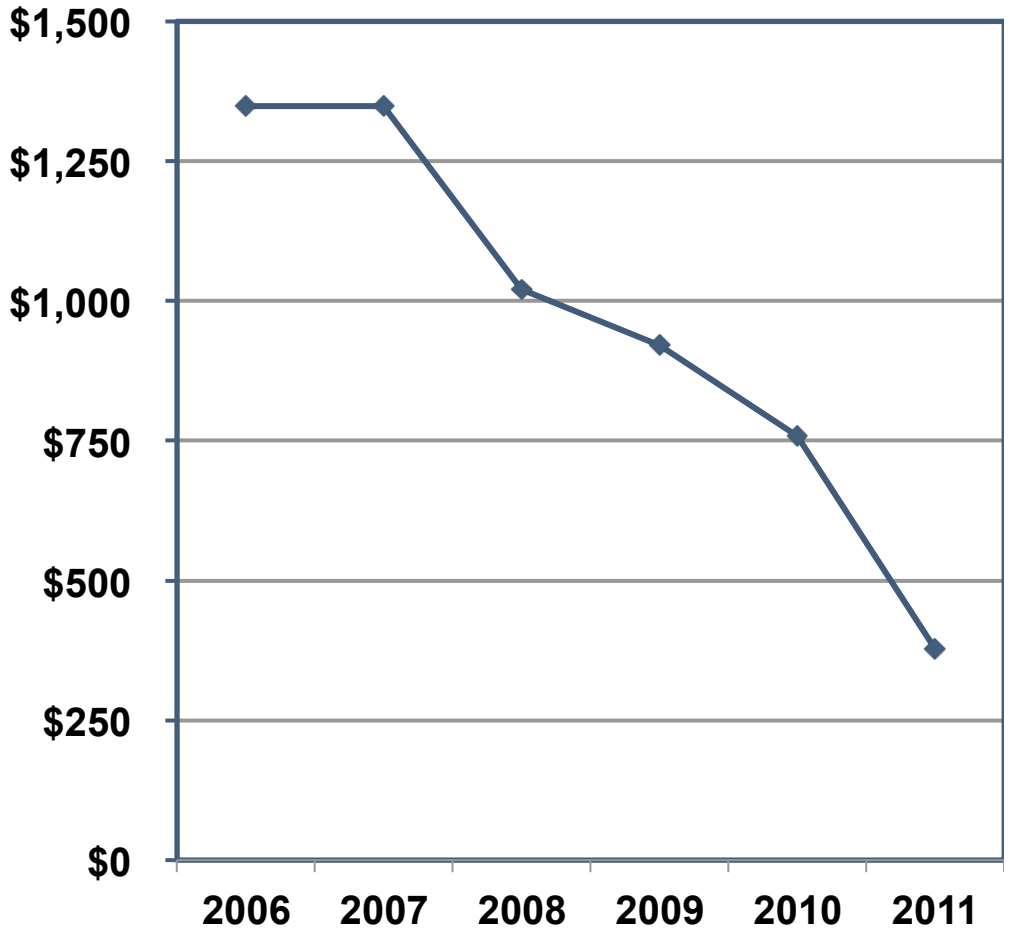
"It follows similar moves by GlaxoSmithKline and AstraZeneca."

Venture Capital (VC) Funding for Neurotherapeutics is Declining

$380M in 2011, most of which is going to:

- Clinical stage drugs spun out of pharmas
- Re-purposing of generic drugs

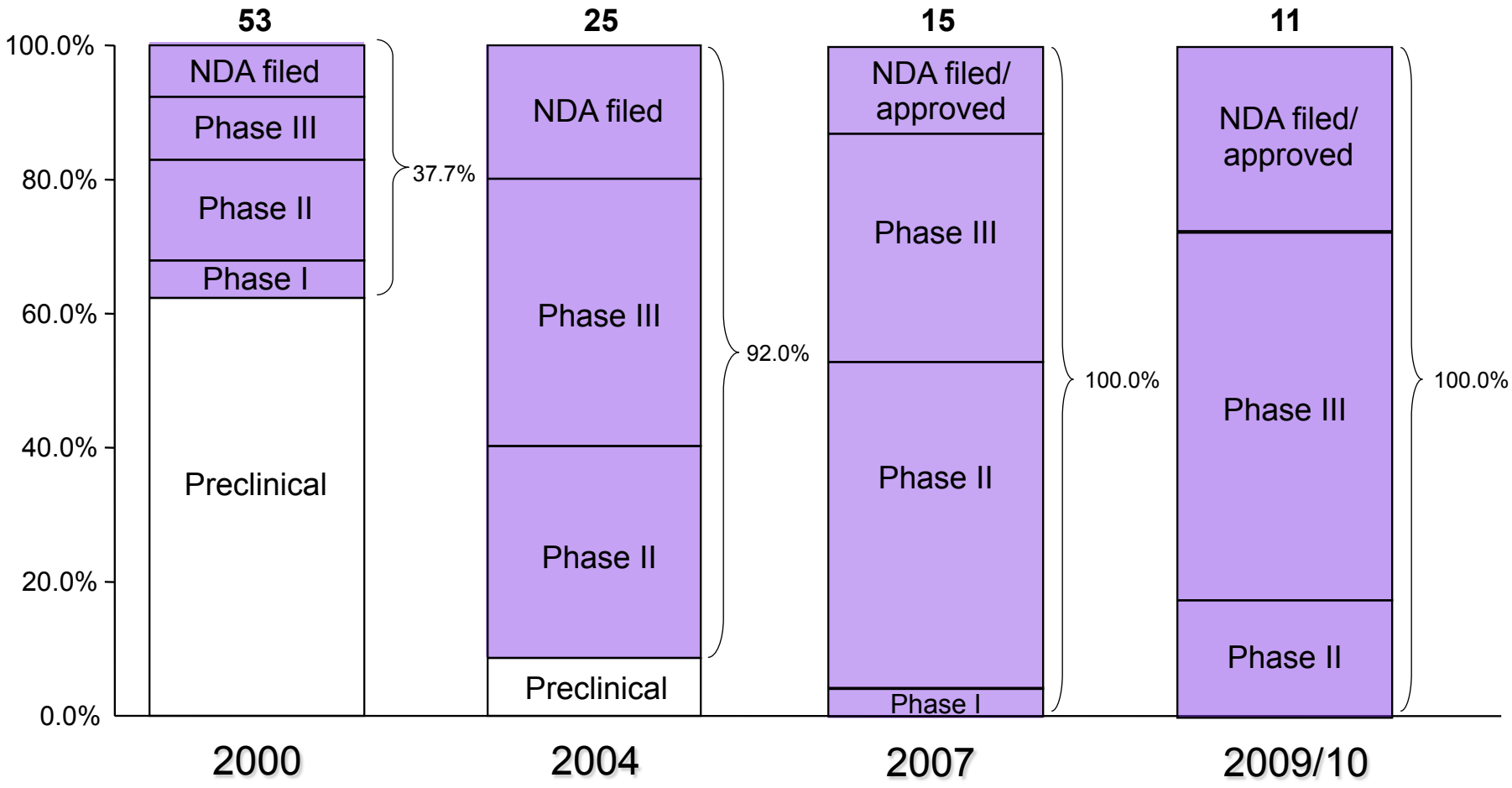
Overall, there is less funding for discovery stage CNS diseases



U.S. Biotech VC funding is stable but the focus is on later stage

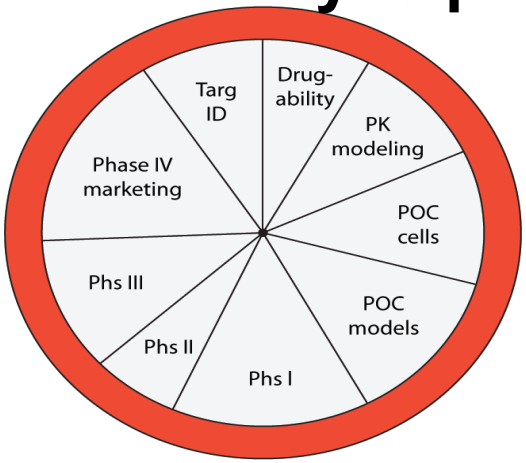
Appetite for risk is decreasing

Biotech IPOs as Indicator of Industry Trends

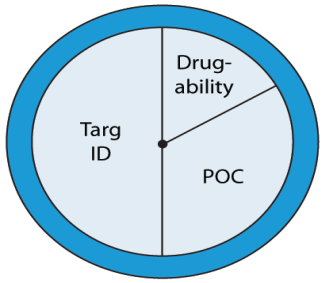


Johnston Blakely & Company (www.johnstonblakely.com)

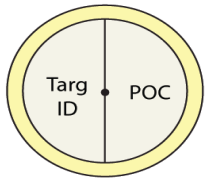
Industry is pursuing new models – eliminate silos



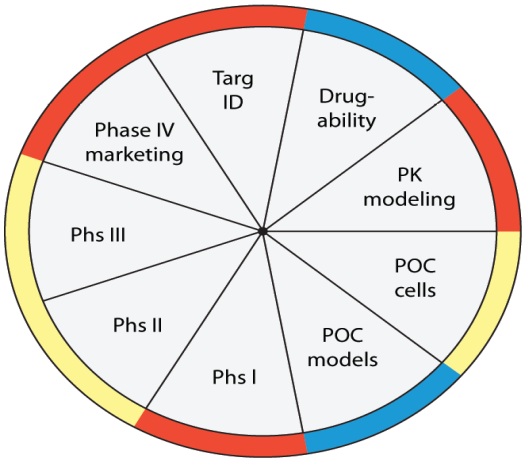
Pharma



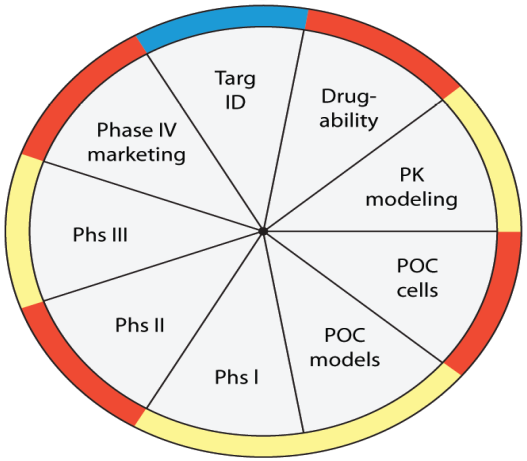
Biotech



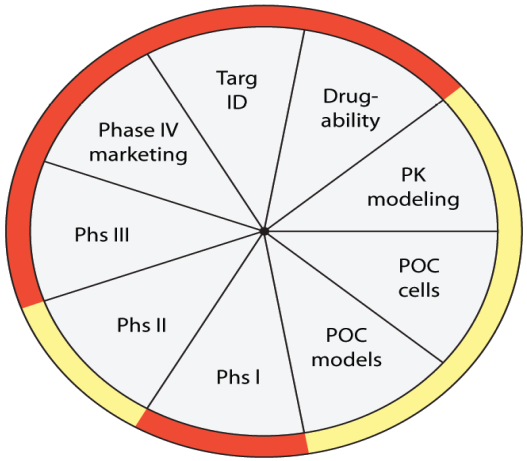
Academia



Project 1

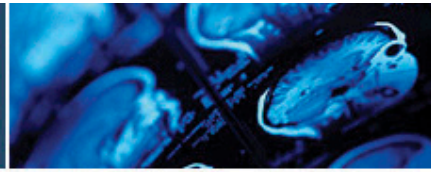


Project 2

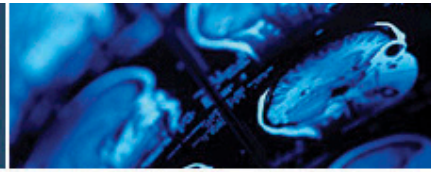


Project 3

Carsten Skarke and Garret A. FitzGerald, Science Translational Medicine April 2010



What should NINDS's role be in this changing climate?



Office of Translational Research (OTR)

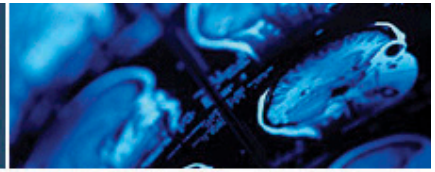
Mission: To facilitate the preclinical discovery and development of new therapeutic interventions for neurological disorders

Bench

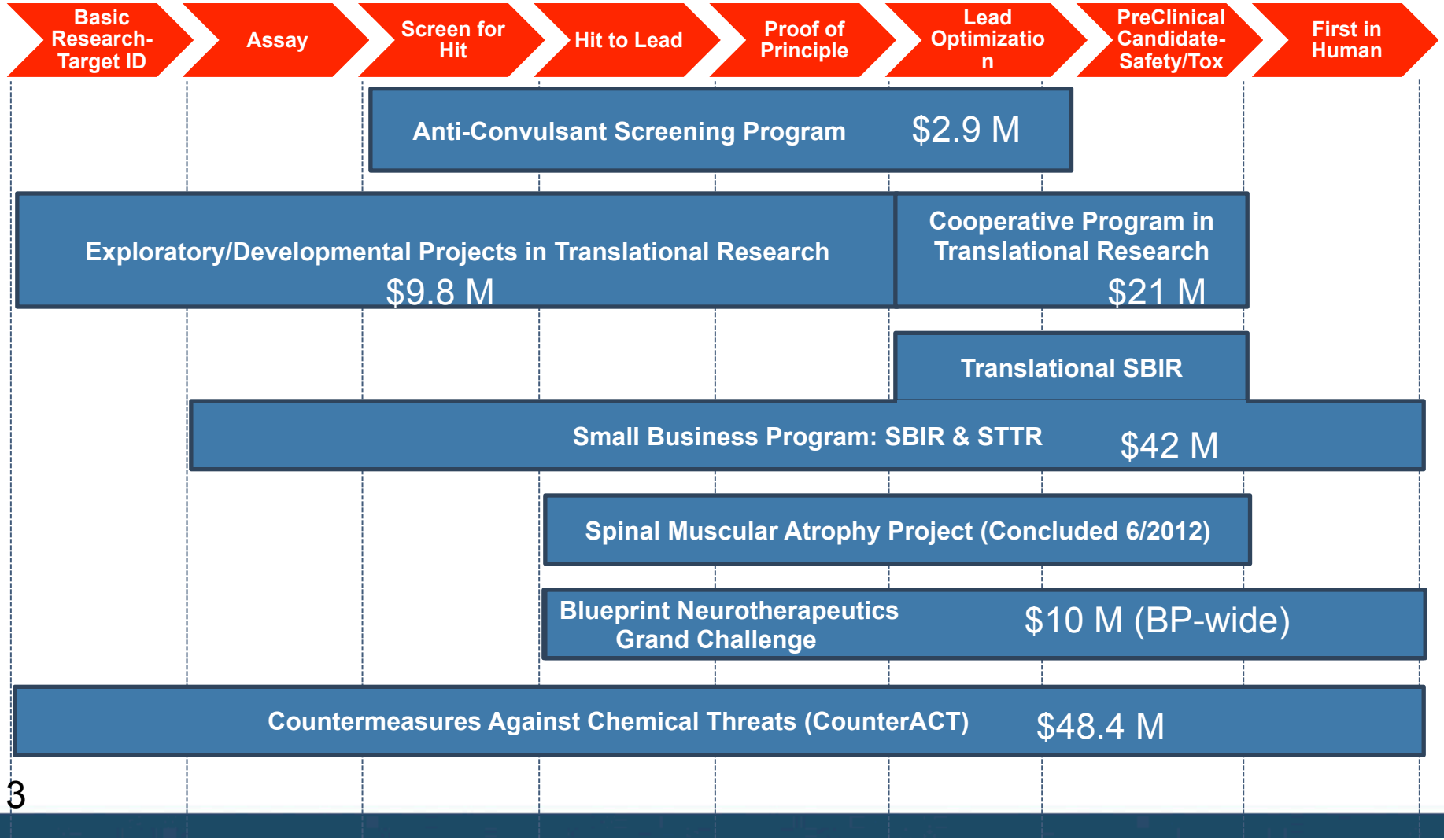
Preclinical

Patients

National Institute of Neurological Disorders and Stroke



OTR uses a Variety of Approaches for Translation



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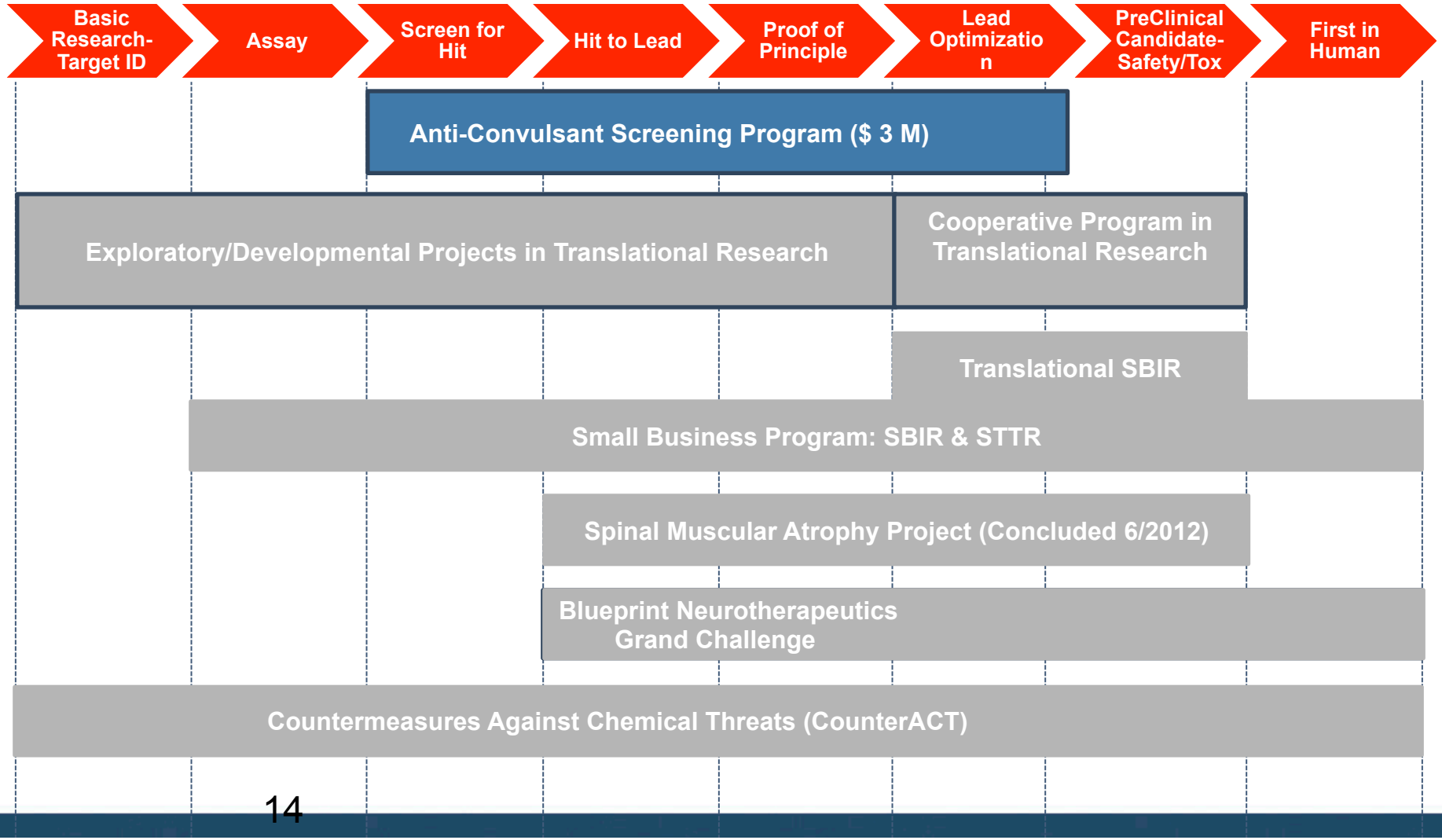
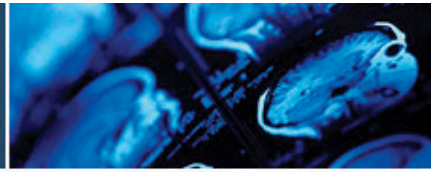


NINDS Anticonvulsant Screening Program (ASP)

Approach: Provide services and expertise to investigators developing anticonvulsants

- Established in 1975 (Dr. Steve White: PI, Univ. of Utah)
- Screening performed via a contract mechanism using a battery of seizure models
- Second track added in 2007 for chemical nerve age countermeasures
- NINDS staff report results to participants, advise on future development
- Supplier retains IP
- Role in 10 marketed drugs since 1990

John Kehne

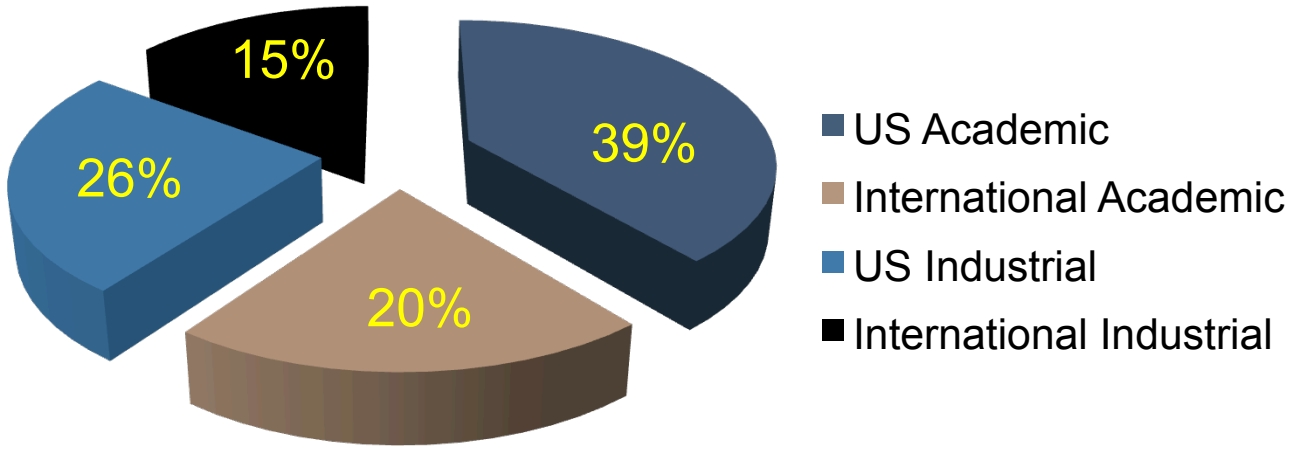


Marketed Drugs 1990 to Present

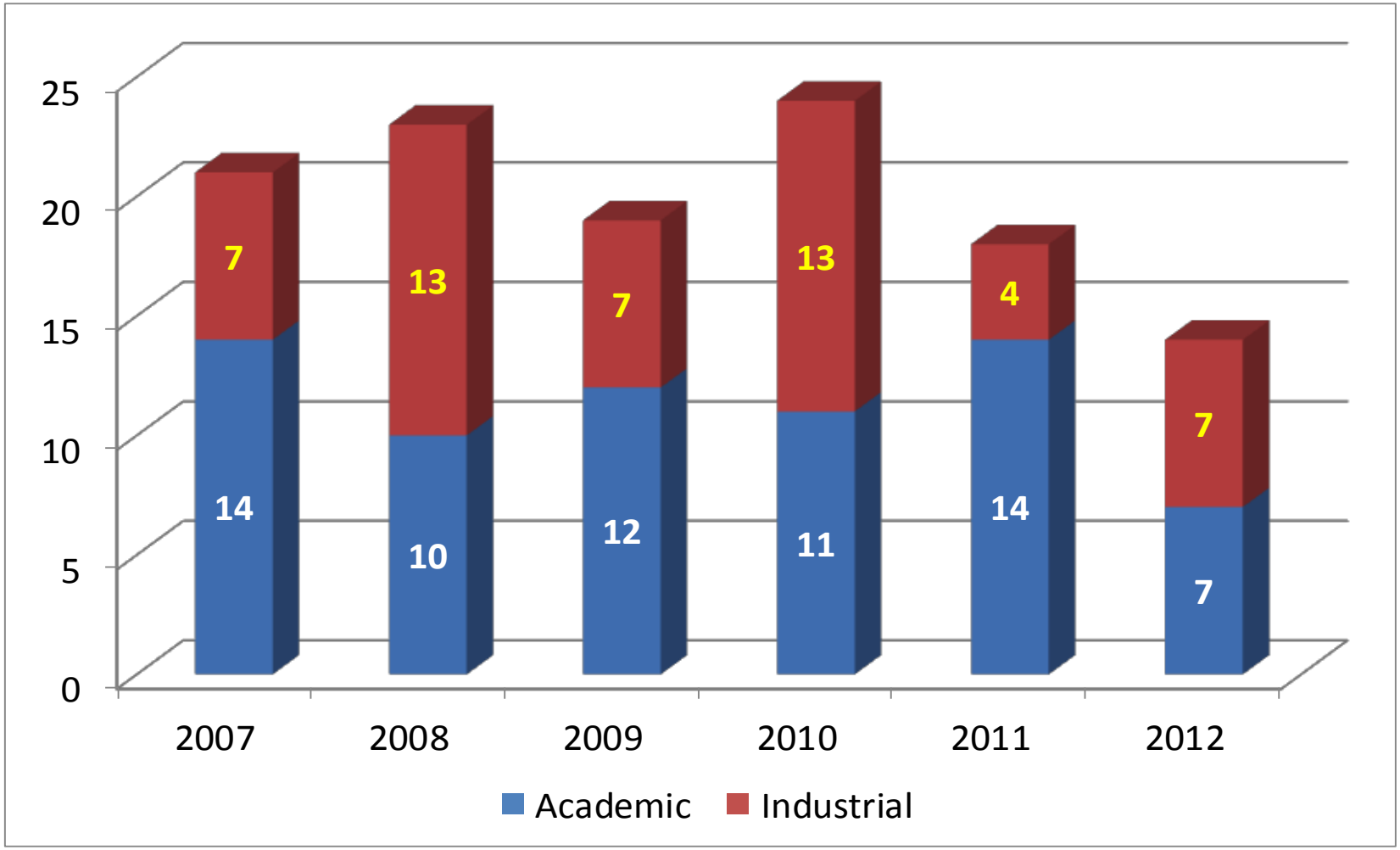
Drug	ASP Contribution	Year Approved
Felbamate	Major	1993
Gabapentin	Minor	1993
Lamotrigine	Minor	1994
Topiramate	Major	1996
Levetiracetam	Minor	1999
Oxcarbazepine	Early	2000
Lacosamide (Vimpat)	Major	2008
Rufinamide (Banzel)	Early	2008
Vigabatrin	Minor	2009
Ezogabine (Potiga)	Minor	2011

ASP Participants

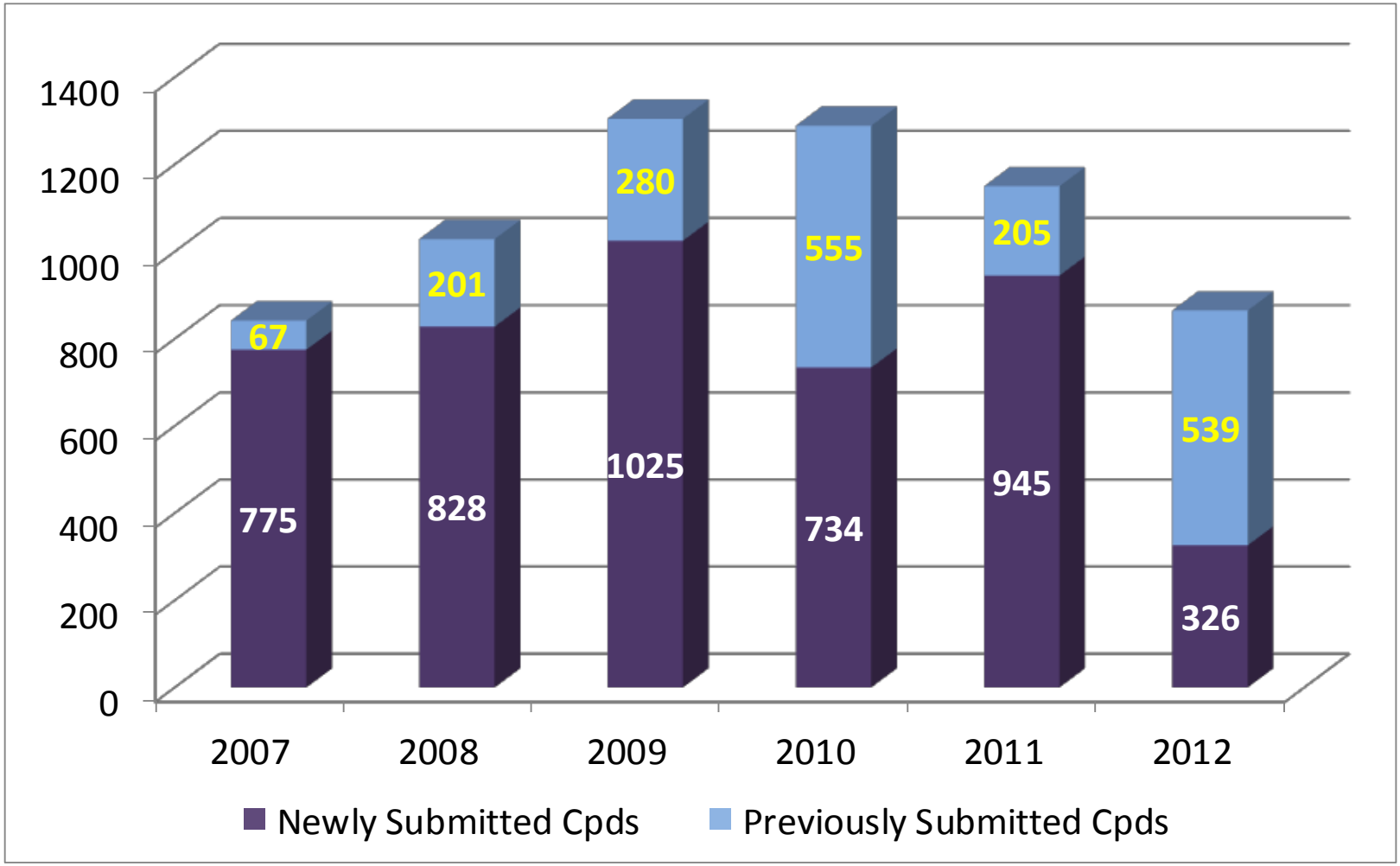
- 547 Total Projects
- 318 Academic Participants
- 226 Industrial Participants
- 3 Government Participants
- 37 Countries



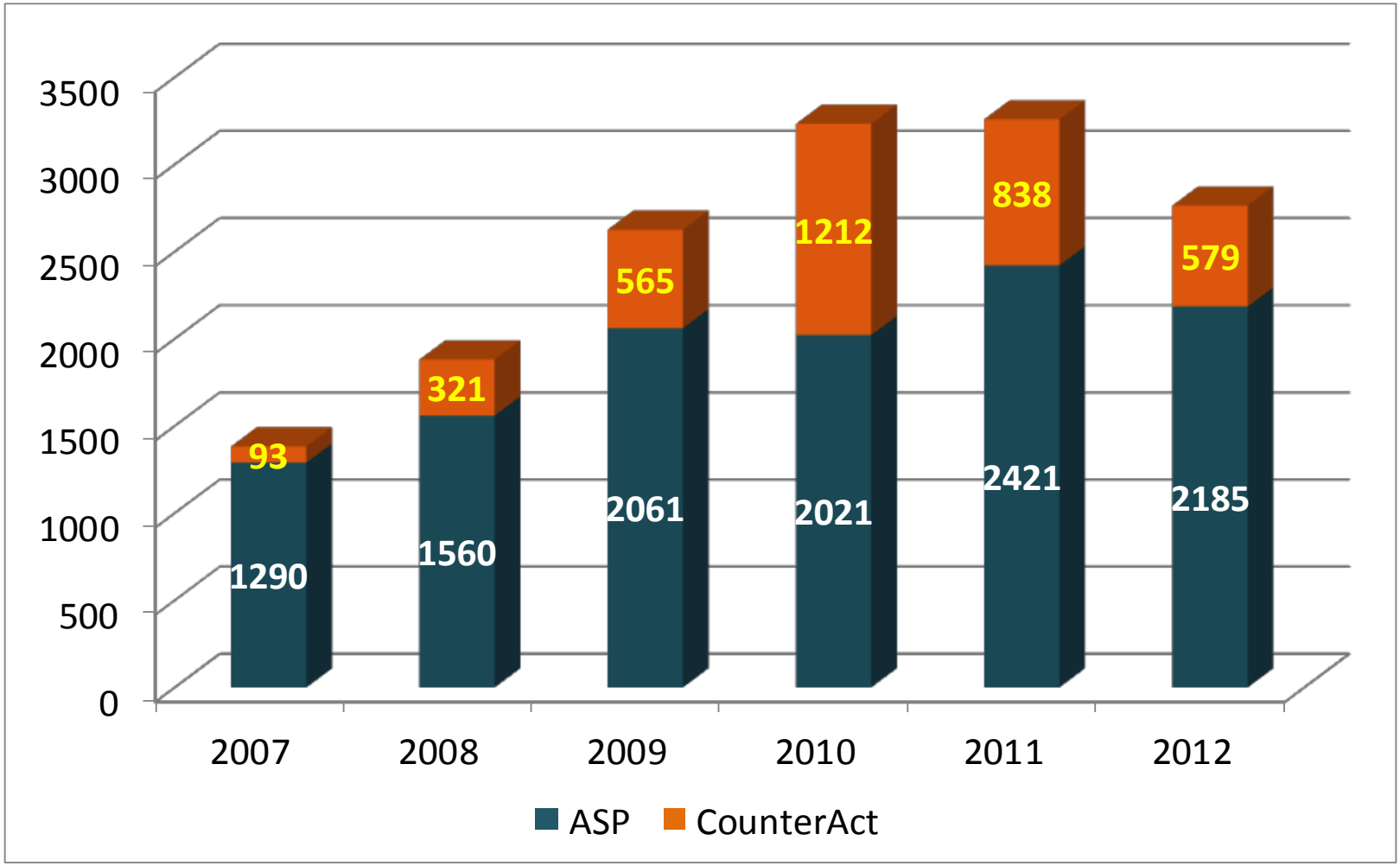
New ASP Participants per Year

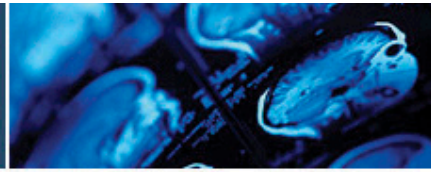


Compounds Tested by ASP



Tests Conducted by ASP





ASP Working Group

- Considered ASP's value to epilepsy research and drug development within the current scientific and pharmaceutical landscape
- Made recommendations for future of the program (focus, strategies, and configuration)
- Presented final report on February 16, 2012

Robert E. Pacifici, PhD, *Chair*
CHDI Management/CHDI Foundation

Susan Axelrod
Citizens United for Research in Epilepsy

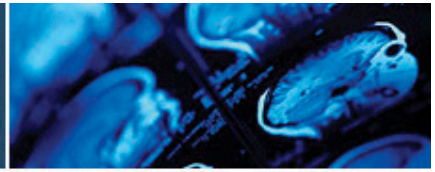
Amy Brooks-Kayal, MD
Children's Hospital Colorado

Henrik Klitgaard, PhD
UCB Pharma

James McNamara, MD
Duke University

Jeffrey L. Noebels, MD, PhD
Baylor College of Medicine

Roy Twyman, MD
Johnson and Johnson



ASP Working Group Report

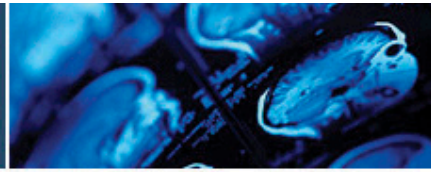
ASP has facilitated the development new AEDs

However, challenges remain:

- Treatment-resistant epilepsy
- No treatments modify disease course or prevent its development
- Poor side-effect profiles

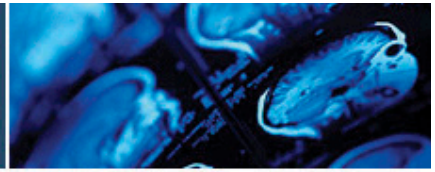
Therefore, the ASP should

- address the most critical unmet needs
- adapt to new landscape



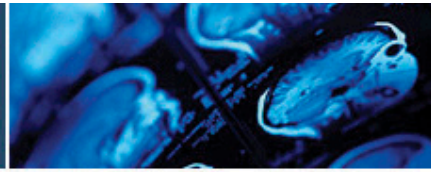
Progress on Selected ASP Working Group Recommendations

- Revise focus
- Reshape, integrate
- Refine operating procedures
- Select or develop new models



ASP Working Group Implementation Progress

- Revised requirements for entry
- Developed quality control measures for compound purity and identity
- Improved communication with University of Utah ASP scientists
- Integrated ASP into NINDS epilepsy research program
- Initiated ASP leadership recruitment
- Improved coordination between ASP and CounterACT



Recent ASP Success Story

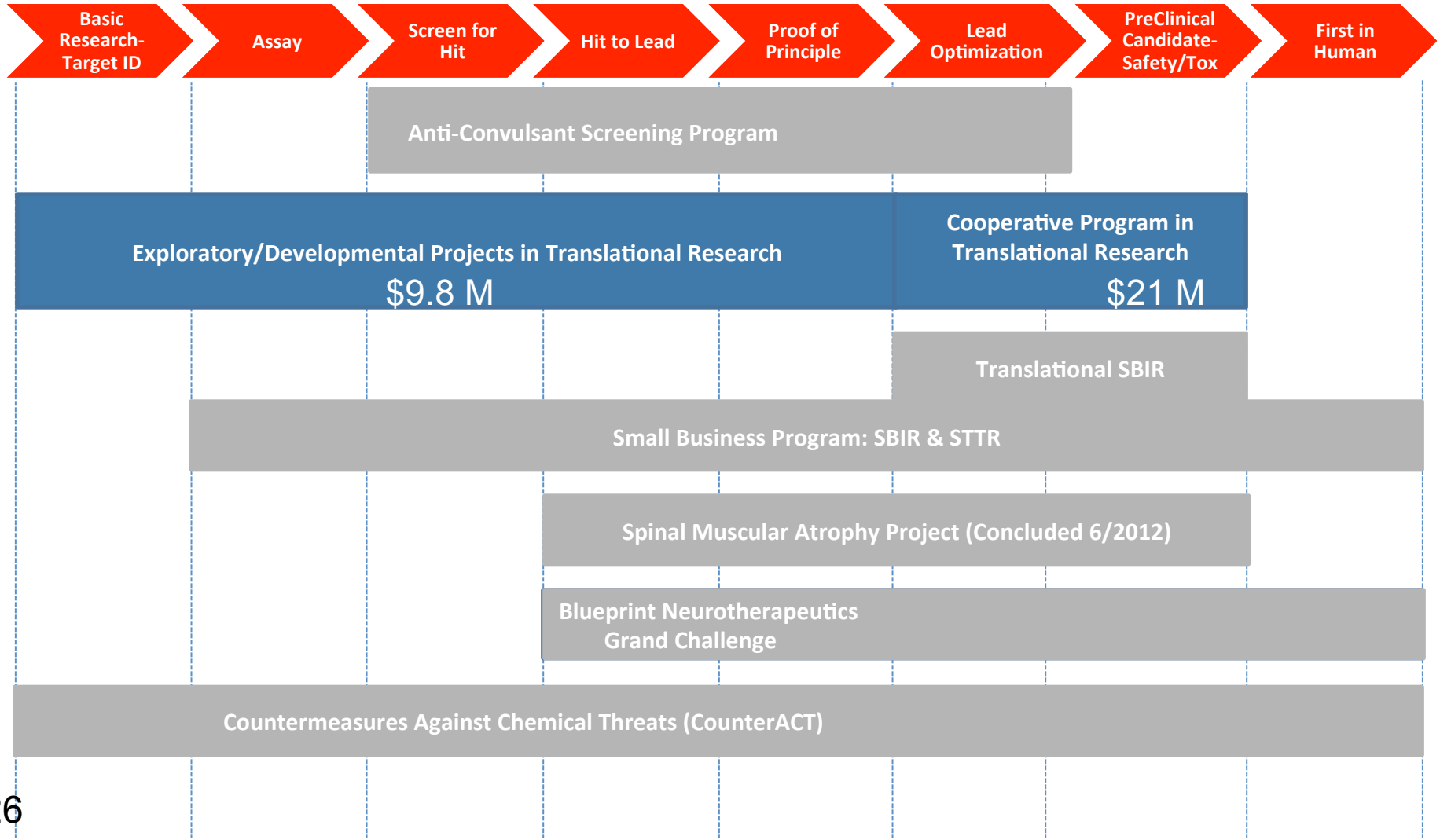
- Vigabatrin (Sabril), a GABA aminotransferase (GABA-AT) inhibitor, approved for infantile spasms (IS) and refractory complex partial seizures (2009)
- CPP-115 (Catalyst Pharmaceutical), a more potent inhibitor of GABA-AT, performs better in models of treatment-resistant epilepsy (2009)

Compound	6Hz model*		Corneal kindled mouse Model*
	32 mA	44 mA	
Vigabatrin	23 mg/kg	154 mg/kg	80 mg/kg
CPP-115	5.2 mg/kg	28 mg/kg	20 mg/kg

* ED50 values

- CPP-115 started Phase I trial in late 2011, potentially provides a better treatment for IS and refractory epilepsy

OTR uses a Variety of Approaches for Translation



NINDS Exploratory Projects and Cooperative Program in Translational Research

Linda McGavern, PhD
Program Manager

Christina Vert, MS
Program Analyst

Cooperative Program Purpose and Goals

- Program launched in 2002 and includes drugs, biologics, and devices
- Purpose: To stimulate preclinical development of therapeutics in non-profit and small business sectors
- Features: Special review, milestone-based decisions

Translational Program Overview

Mechanisms	tR21	U01	U44
Description	Support projects through IND/IDE submission Support prior to or in parallel with U01	Support projects through IND/IDE submission	Support SBIR projects in various phases
Budget	$500,000 over 2 years	$1 million per year direct costs, up to 5 years	Up to $7 million total costs, over 5 years
Risk	High	Milestone driven to mitigate risk	Milestone driven to mitigate risk
(Active FY12) Total Awarded	(58) 180	(31) 48	(14) 16
FY12 Dollars	$9.8 M	$26 M	$ 9.7 M

The tR21 Program is for Exploratory Translational Science

- Originally intended as an entry for the U01 program
- Examples of exploratory activities:
  - Development of screening assays and models
  - SAR and pre-clinical work
  - Development of animal models for testing therapeutic target engagement
  - Development of biomarkers
- Not for:
  - Basic research animal models
  - Diagnostics
  - Tool compounds

The U01 Program is for Translational Science

- Investigators work with NIH staff to develop goals and milestones
- Activities include:
  - Preclinical efficacy testing
  - Predictive ADME *(absorption, distribution, metabolism, and excretion)*
  - Toxicology testing
  - IND/IDE submission
  - Phase 0 clinical trials

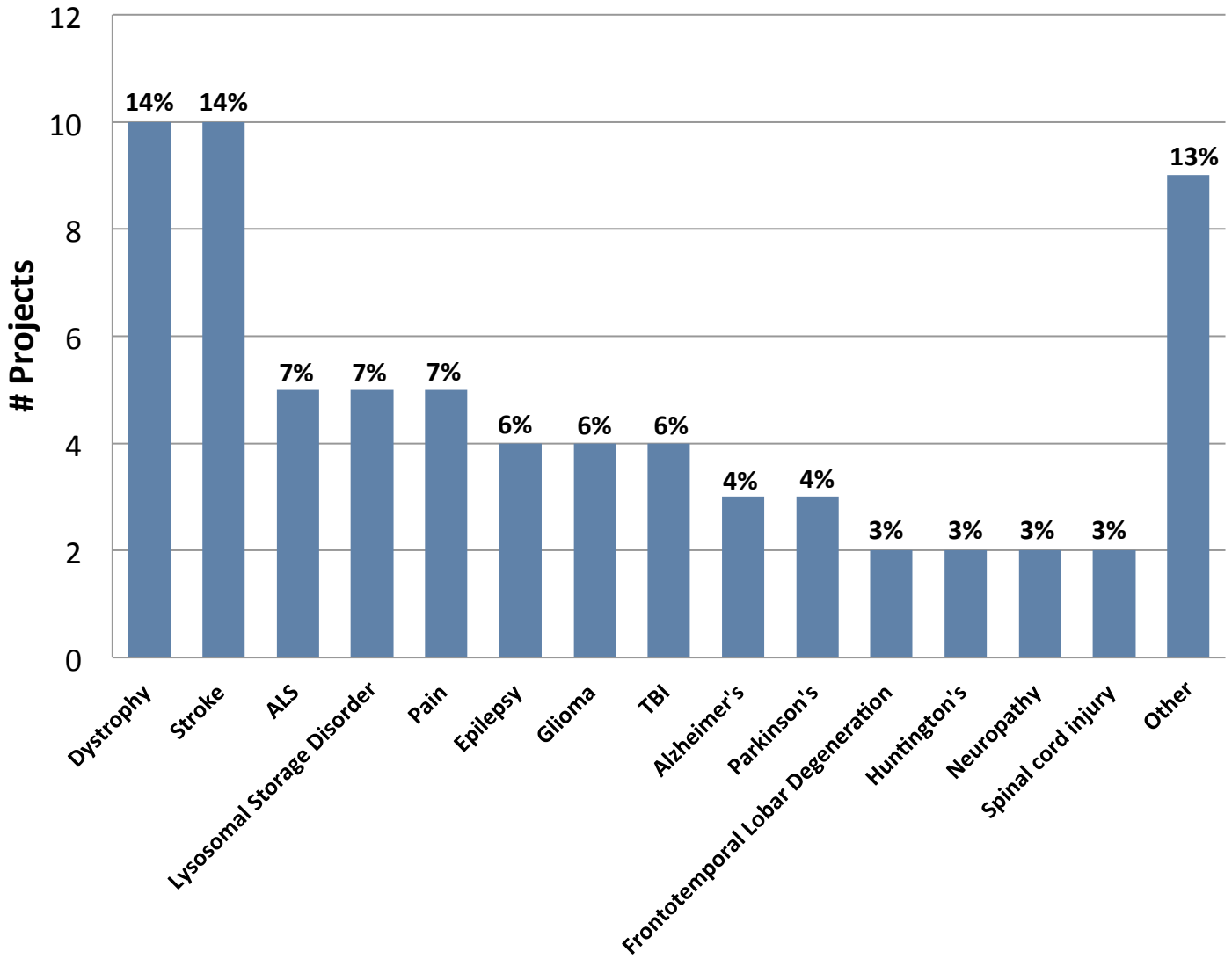
U01 Entry Criteria

- Projects must identify a therapeutic lead and should provide *in vivo* proof-of-concept efficacy data
- Projects lacking efficacy models must have *in vivo* models that include measurement of a pharmacodynamic biomarker for the intended therapeutic using clinical route of administration
- Device projects must have a clinically meaningful outcome based on clinician and patient input

Additional Review Considerations

- Rigor
- Overall plan for therapy development
- Intellectual property

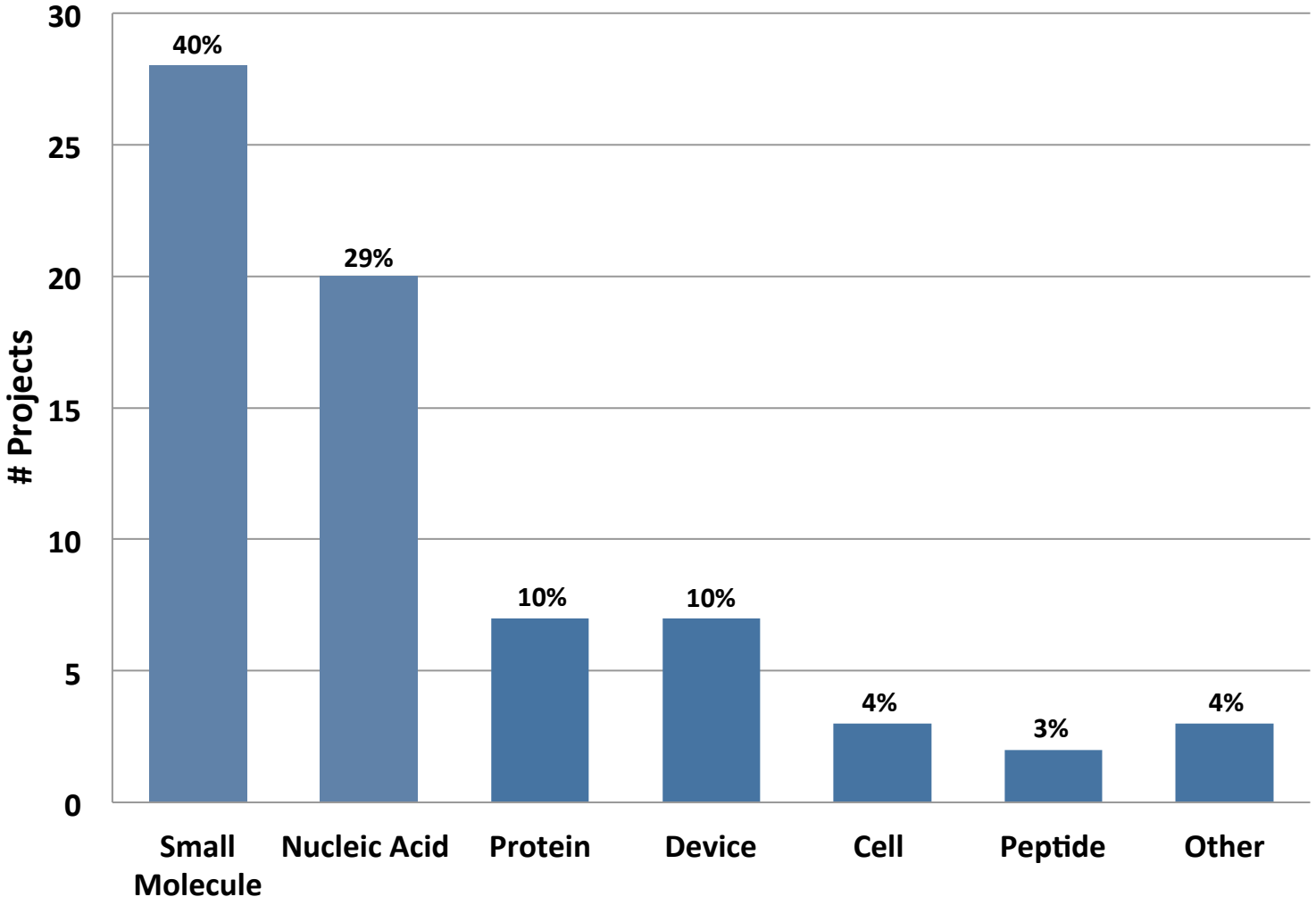
Portfolio (n=70) by Indication (2002-2012)



Other:

Batten disease
Down Syndrome
Neurodegeneration
Neurofibroma
Insecticide poisoning
Peripheral nerve injury
Phenylketonuria
SMA
Spinal and Bulbar Muscular Atrophy

Portfolio (n=70) by Interventional Modality (2002-2012)



Other:
Vaccine
Dog Center
Drug Discovery Center

Projects are Reaching Definitive Endpoints

- 16 achieved intended goal:
  - 9 U01s, 2 U44s, 4 U54s, 1 U24 (6 have filed 1+ INDs)
- 11 discontinued (since 2008)
  - 8 U01s, 2 U44s, 1 U24
  - Reasons:
    - Didn't pursue studies proposed in application or milestones (1)
    - Didn't meet milestones for efficacy criteria (6) or other advancement criteria (3)
    - Achieved IND ahead of schedule (1)

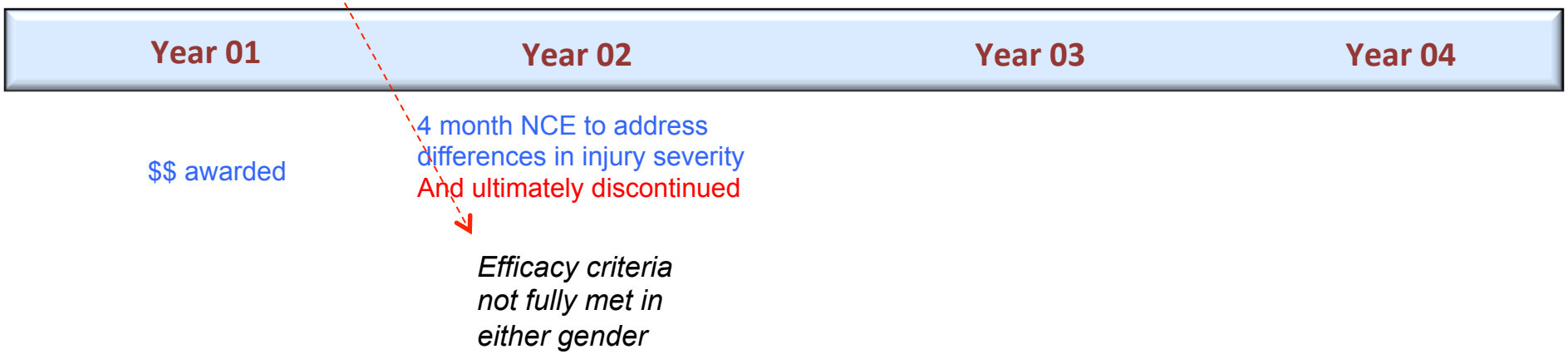
Translational Projects Reaching IND and Beyond

Principal Investigator	Institution	Disorder	Therapeutic Approach	Project End Date	Clinical Trial
Ralph Snodgrass	Vistagen Therapeutics, Inc.	Epilepsy / Neuropathic Pain	Drug	2008	Phase I
Howard Federoff	Georgetown University Medical Center	Parkinson's	Nucleic Acid Therapy	2009	Phase I
Xiao Xiao	University of North Carolina	Duchene Muscular Dystrophy	Nucleic Acid Therapy	2009	Phase I
Cesario Borlongan	University of South Florida	Stroke	Cell Therapy	2009	Phase II
Ronald Crystal	Weill Medical College – Cornell University	Batten Disease	Nucleic Acid Therapy	2010	Phase I/II
Guohua Xi	University of Michigan	Stroke	Drug	2012	Phase II

Case Study #1

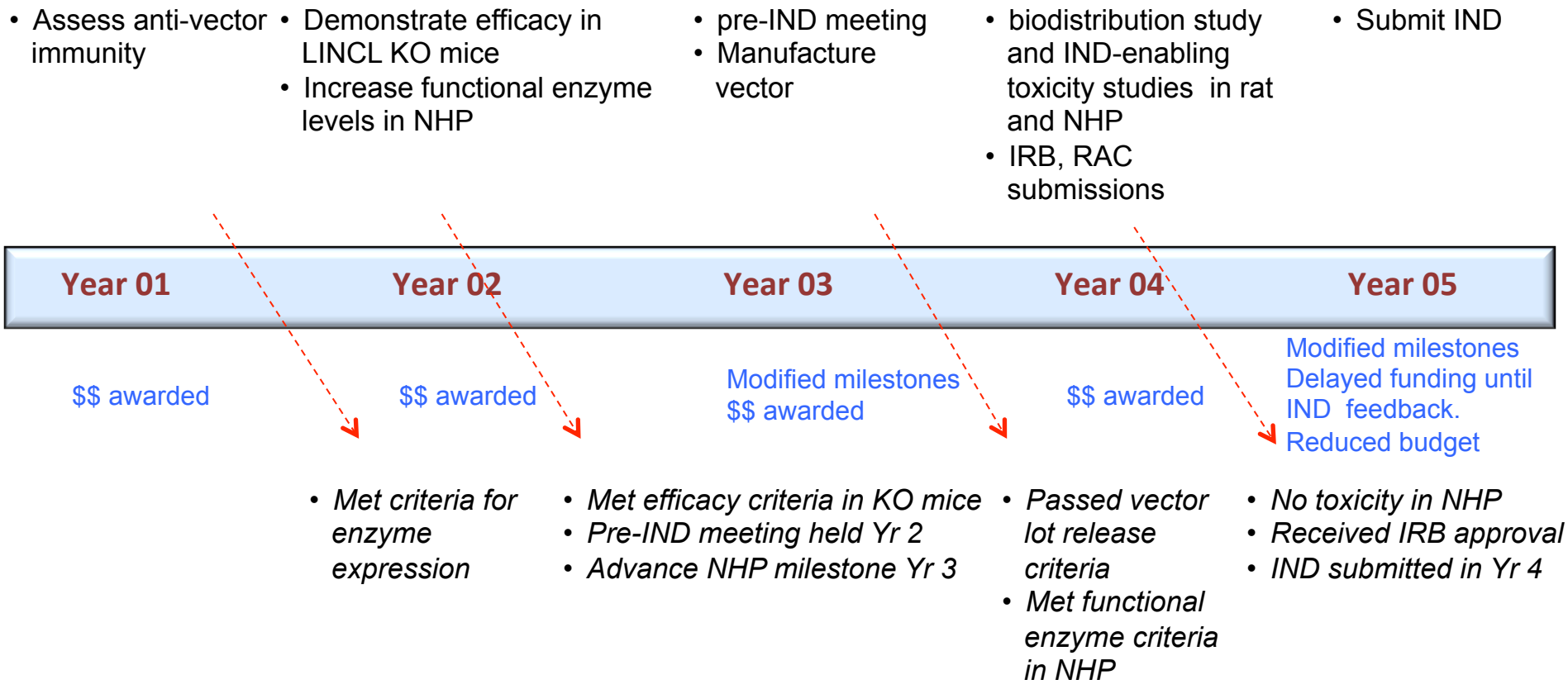
Mitochondrial inhibitor to treat acute spinal cord injury (SCI)

- Demonstrate recovery in a severe SCI model in either gender
- PK to determine treatment regimen
- Improve mitochondrial function in animals
- Demonstrate motor and sensory recovery
- pre-IND meeting
- Submit IND



Case Study #2

Gene therapy to treat Batten Disease / late infantile neuronal ceroid lipofuscinosis (LINCL)



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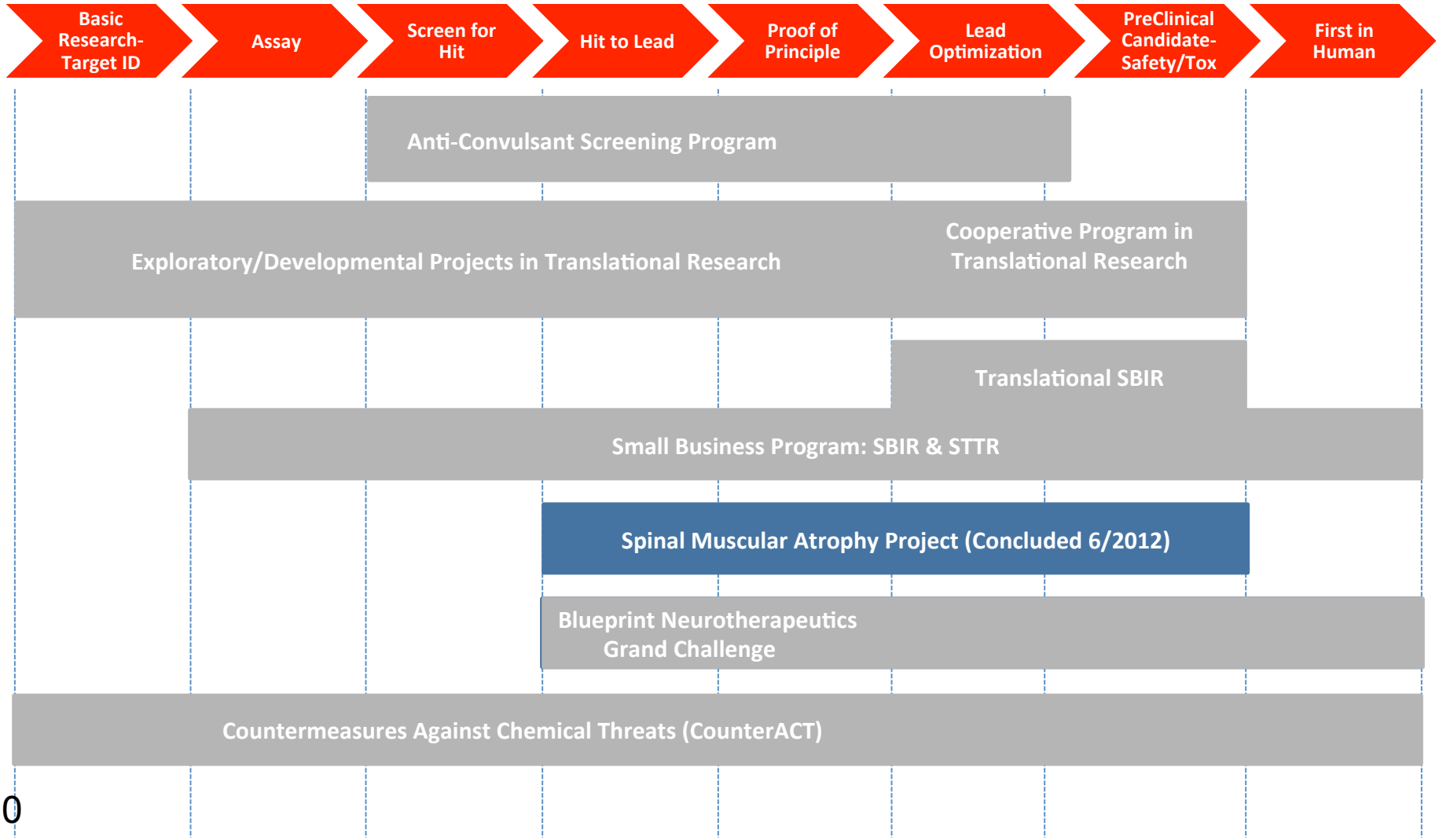

The Spinal Muscular Atrophy Project

- SMA: Approx. 10,000 US patients, with variable severity
- Project spent $32 Million via a contracted network of CROs and researchers (2003-2012)
- Considered small molecules, biologics, gene therapy and stem cell therapeutic approaches and settled on small molecules

From Indoprofen to Therapeutic Candidate

- In 2005, started med. chem. using indoprofen
- By 2011, had late-lead optimization/pre-development candidate
  - Robust activity in SMA patient fibroblasts with EC_{50} of 10 nM
  - In C/C SMA mice increased SMN protein levels significantly; poor solubility limited exposure and effect in brain, and limited efficacy in Delta7 SMA mouse model

SMA Project Partnering Activities

Targeted marketing of ALB-111 began July 2012

- Primary Goal: Identify drug development partners
- Secondary Goal: Determine if ALB-111 meets pharma requirements or what additional studies are needed
- Results: Reached out to 23 companies (13 pharma companies, 7 biotech companies, and 3 VC firms); implemented 2 research agreements (formulation and mice studies)
- Status: 8 ongoing discussions (3 pharma, 3 biotech, 2 VCs); new ALB-111 research results expected by March 2013

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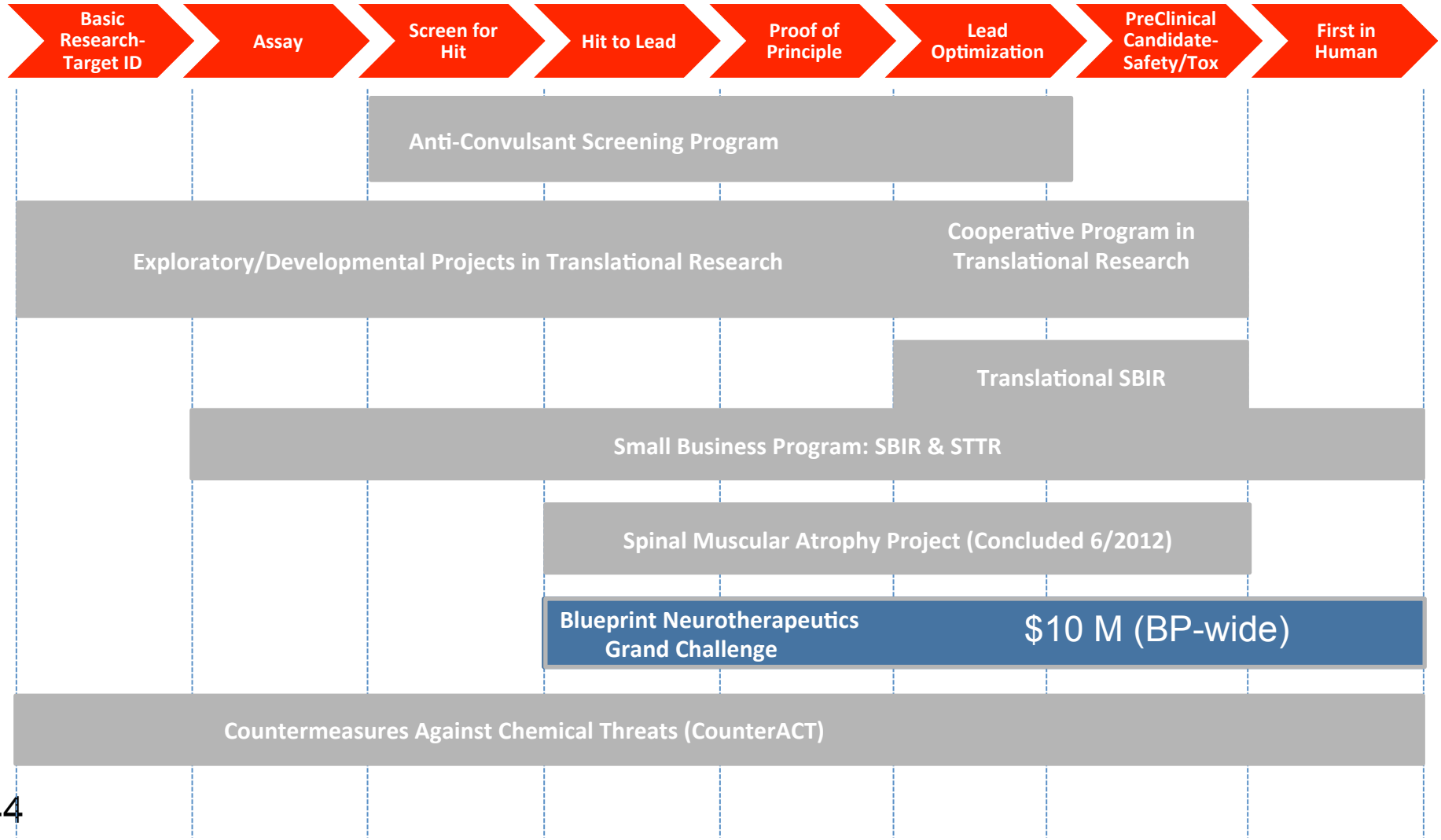


Blueprint Neurotherapeutics Network

Rebecca Farkas, PhD
Program Director

Chuck Cywin, PhD
Program Manager

Amir Tamiz, PhD
Program Manager

Karin French, MS
Program Analyst

The Cooperative Program and SMA Project Informed the Creation of the BPN

Key Features:

- Drug discovery service contractor network
- Biweekly meetings of the lead development teams
- Milestone-based decision-making process
- Prerequisite of a well-validated assay
- Policies on IP ownership established up front
- An independent steering committee advises on milestones and evaluates progress

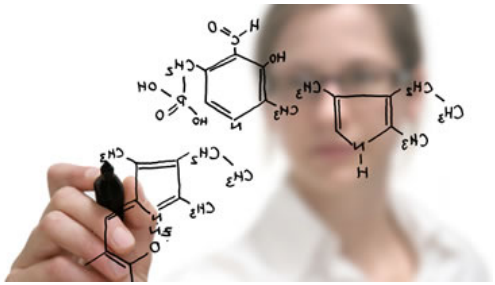
Combining Strengths of NIH and Industry

NIH investigator-initiated ideas

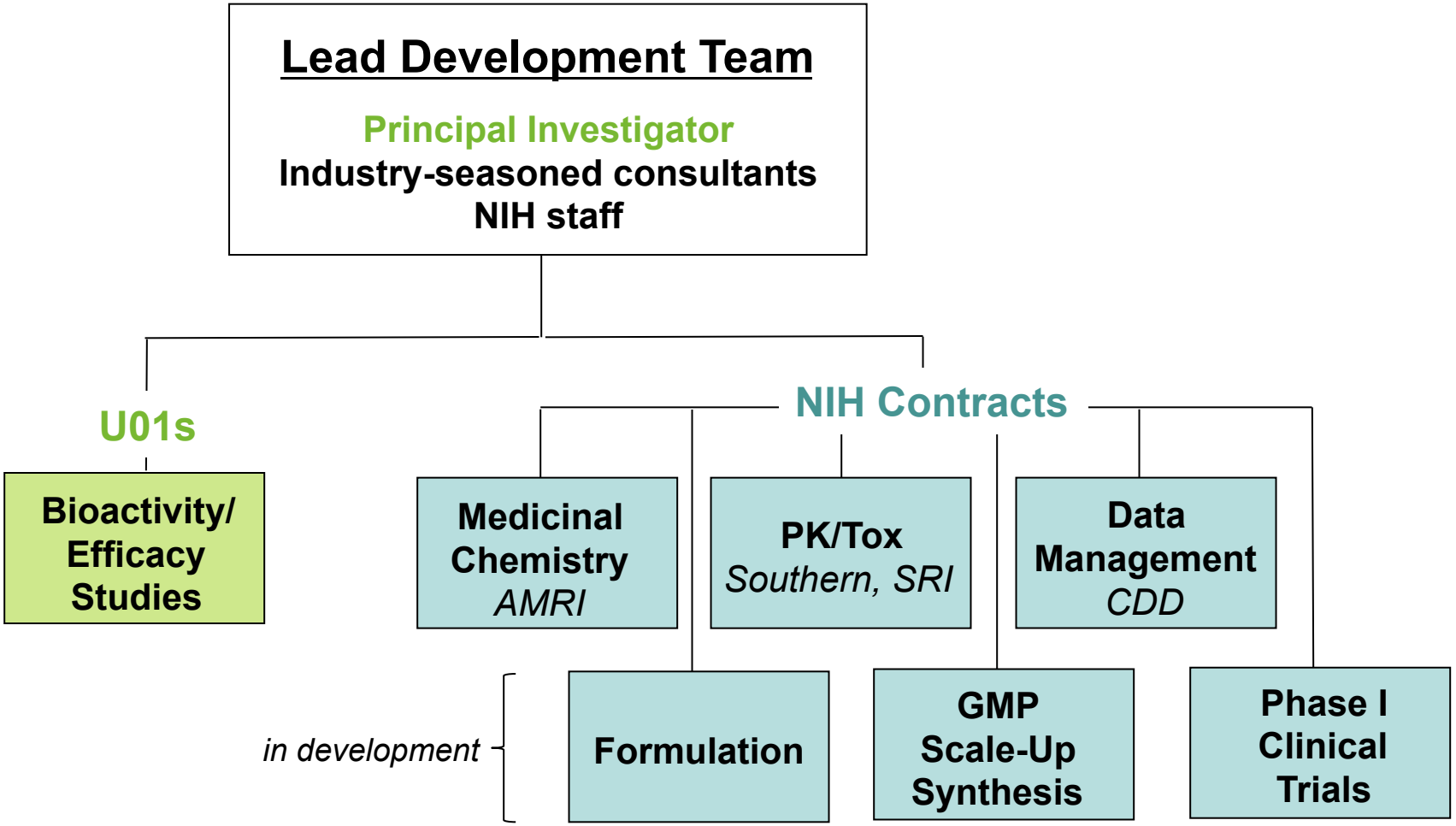
- Novel drug targets
- Strong disease assays and models

Industry expertise

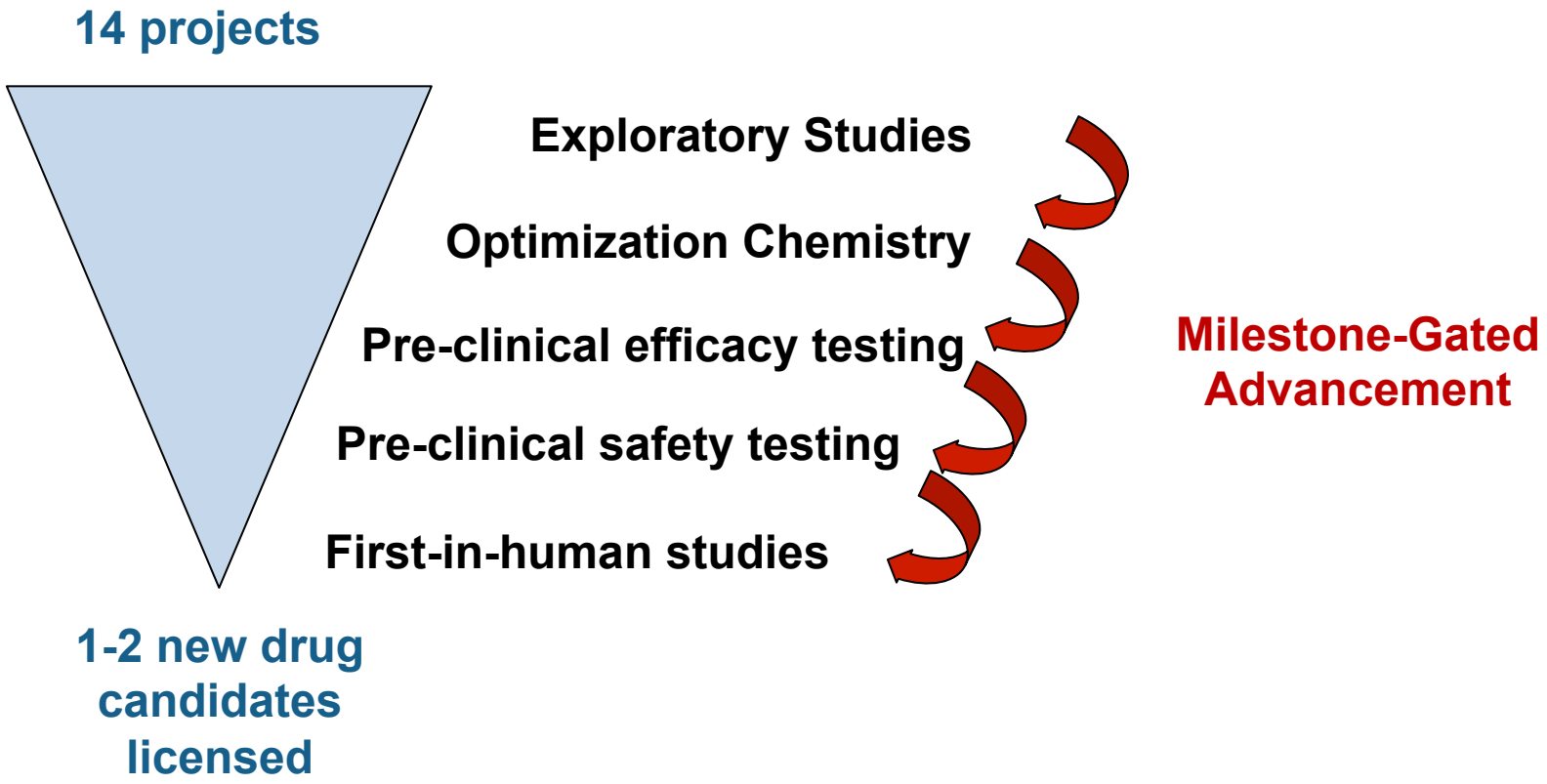
- Advisors with extensive pharma experience
- Industry-standard contract services



"Virtual Pharma" Model



Milestones Used to Fund Most Promising Projects



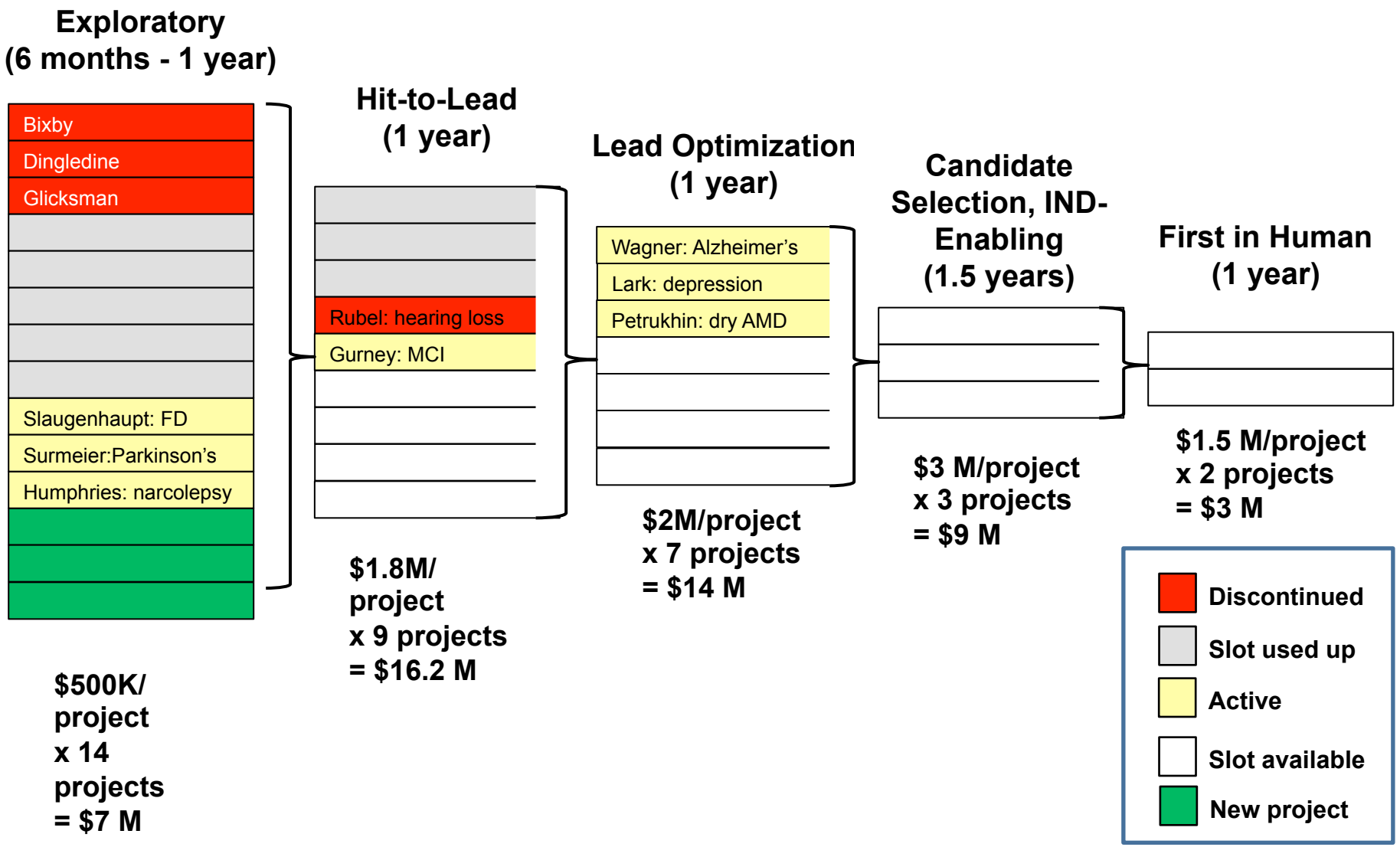
11 Projects Initiated (Jan. 2013)

Principal Investigator	Institution	Disorder
Mark Gurney	Tetra Discovery Partners	Mild Cognitive Impairment
Paul Humphries	Reset Therapeutics	Narcolepsy
Michael Lark	Trevena, Inc.	Depression
Konstantin Petrukhin	Columbia University	Macular Degeneration
Edwin Rubel	University of Washington	Hearing Loss
Susan Slaugenhaupt	Mass. General Hospital	Familial Dysautonomia
D. James Surmeier	Northwestern University	Parkinson's
Steven Wagner	UC San Diego	Alzheimer's
John Bixby	University of Miami	Optic Neuropathy
Raymond Dingledine	Emory University	Stroke
Marcie Glicksman	Brigham and Women's Hospital	ALS

3 projects will launch in mid 2013

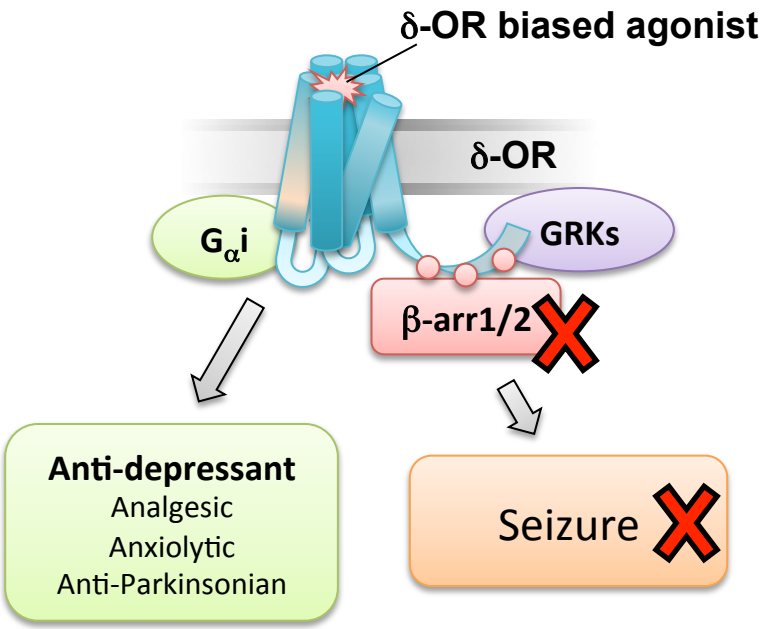
Discontinued

BPN Portfolio (Jan 2013)



A Novel Delta Opioid Receptor Biased Agonist for Major Depressive Disorder

Michael Lark, PhD, Trevena



CENTRAL HYPOTHESIS

δ-OR agonists that activate the G-protein pathway but not the β-arrestin pathway will deliver anti-depressant effects without seizures

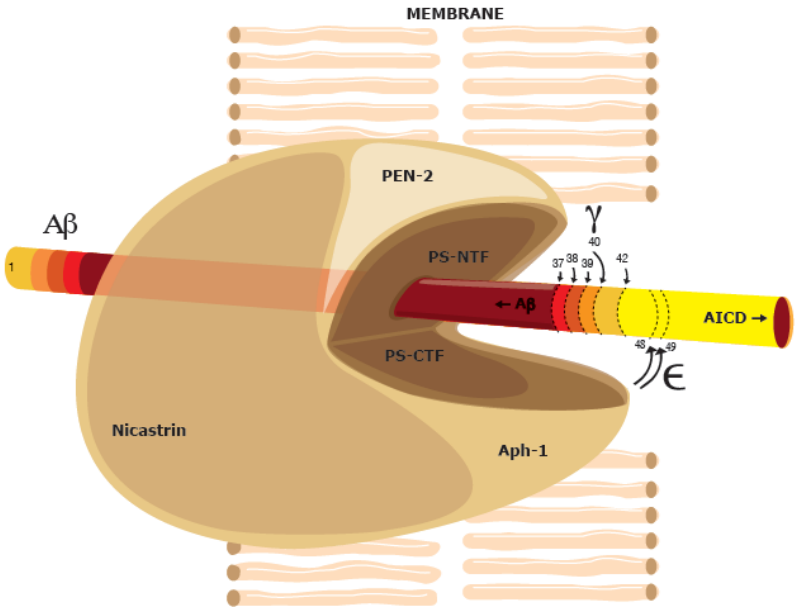
INITIAL CHEMISTRY FOCUS

- Potency (while maintaining bias)
- Rodent bioavailability
- Selectivity against mu and kappa ORs

Jamie Driscoll, Science Officer (NIMH)
Chuck Cywin, PhD, Project Manager (NINDS)

Optimization of Soluble Gamma-Secretase Modulators for Alzheimer's Disease

Steven Wagner, PhD, University of California, San Diego



CENTRAL HYPOTHESIS

Modulators (GSMs) will prevent the production of toxicity-associated Aβ-42 and will lack the negative side-effects observed for inhibitors (GSIs)

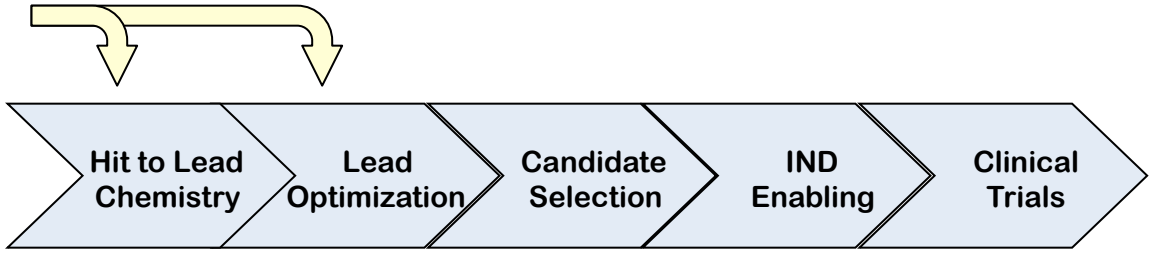
INITIAL CHEMISTRY FOCUS

- Low solubility
- Reactive metabolites

Larry Refolo, PhD, Science Officer (NIA)
Chuck Cywin, PhD, Project Manager (NINDS)

Goal: Advance Projects for Hand-Off

- Strong biological validation
- Compounds amenable to med. chem.
- Robust assays for optimization



- Venture funding
- Industry partnership
- Other grants
- Project conclusion

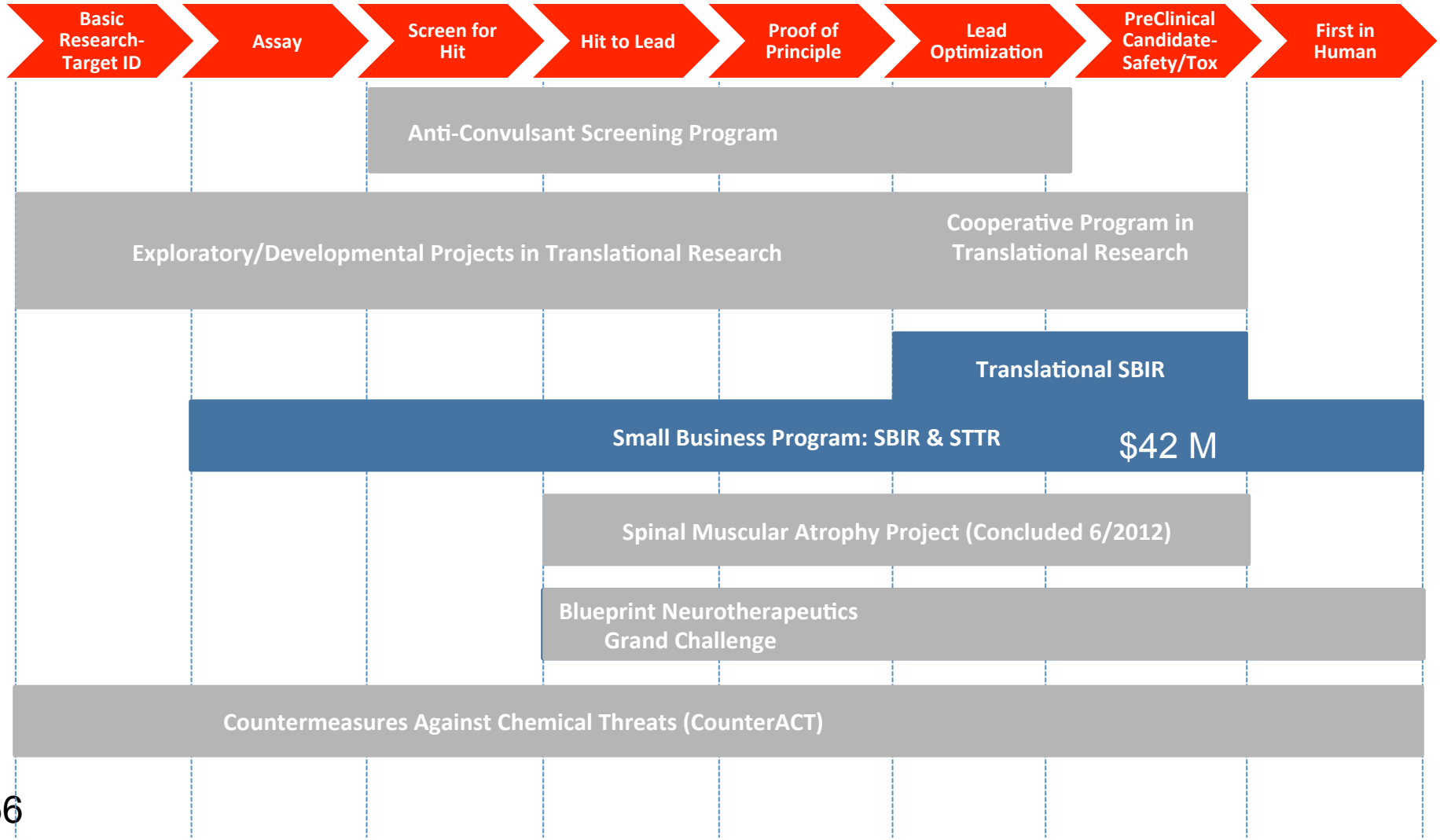
Milestone driven, expert review, industry validation, cost sharing…

Risk decreases as projects successfully advance

BPN: Lessons Learned

- Academics and small companies have different needs, capabilities, and expectations
- Need to think ahead to determine elements of an attractive licensing package and needs for clinical proof-of-concept
  - Molecular markers of drug activity
  - Knowledge of the drug target
  - Intellectual property
- Portfolio perspective influences funding decisions

OTR uses a Variety of Approaches for Translation



NINDS Small Business Programs

Stephanie Fertig, MBA
Program Manager

Becky Roof, PhD
Program Analyst

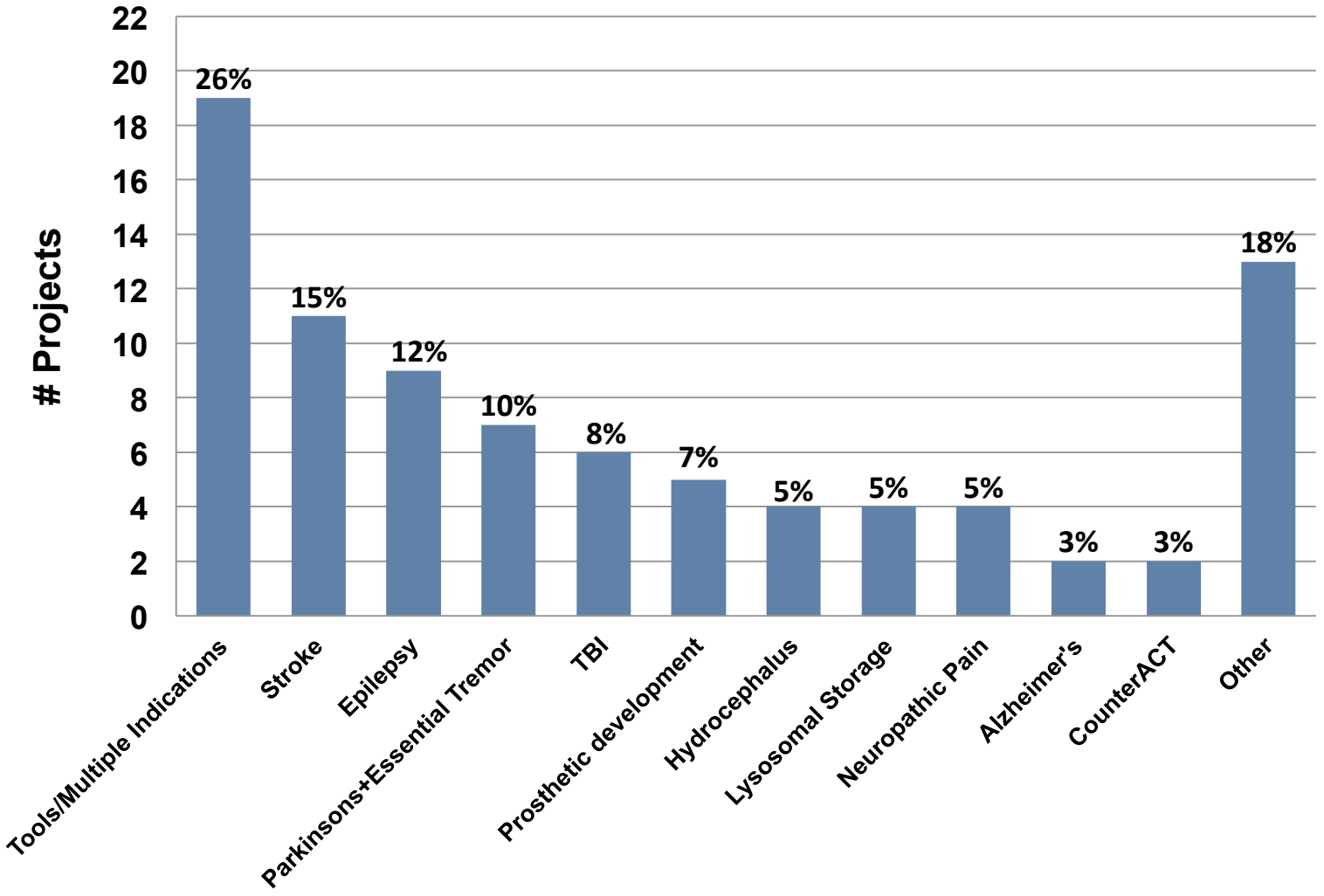
Small Business Program Overview

- Congressionally mandated set-aside programs
- R&D with potential for commercialization
- ~$42M in FY2012 (2.95% of the extramural budget)
- Broad scope
  - Neurotherapeutics, diagnostics, and tools for neuroscience research
  - Bench research, translational research, and early stage clinical trials

Re-Authorization: More Money, Smaller Chunks

Key Provision	Prior Implementation	Re-Authorization
Size of Award (Total Cost)	Phase I: $100-150K, Phase II: $750K- 1M	Phase I: $150K Phase II: $1M
Limits on Award Size	Soft cap	Hard cap
Set-Aside	2.95% (FY2012)	Gradually increase to 3.65% by 2017

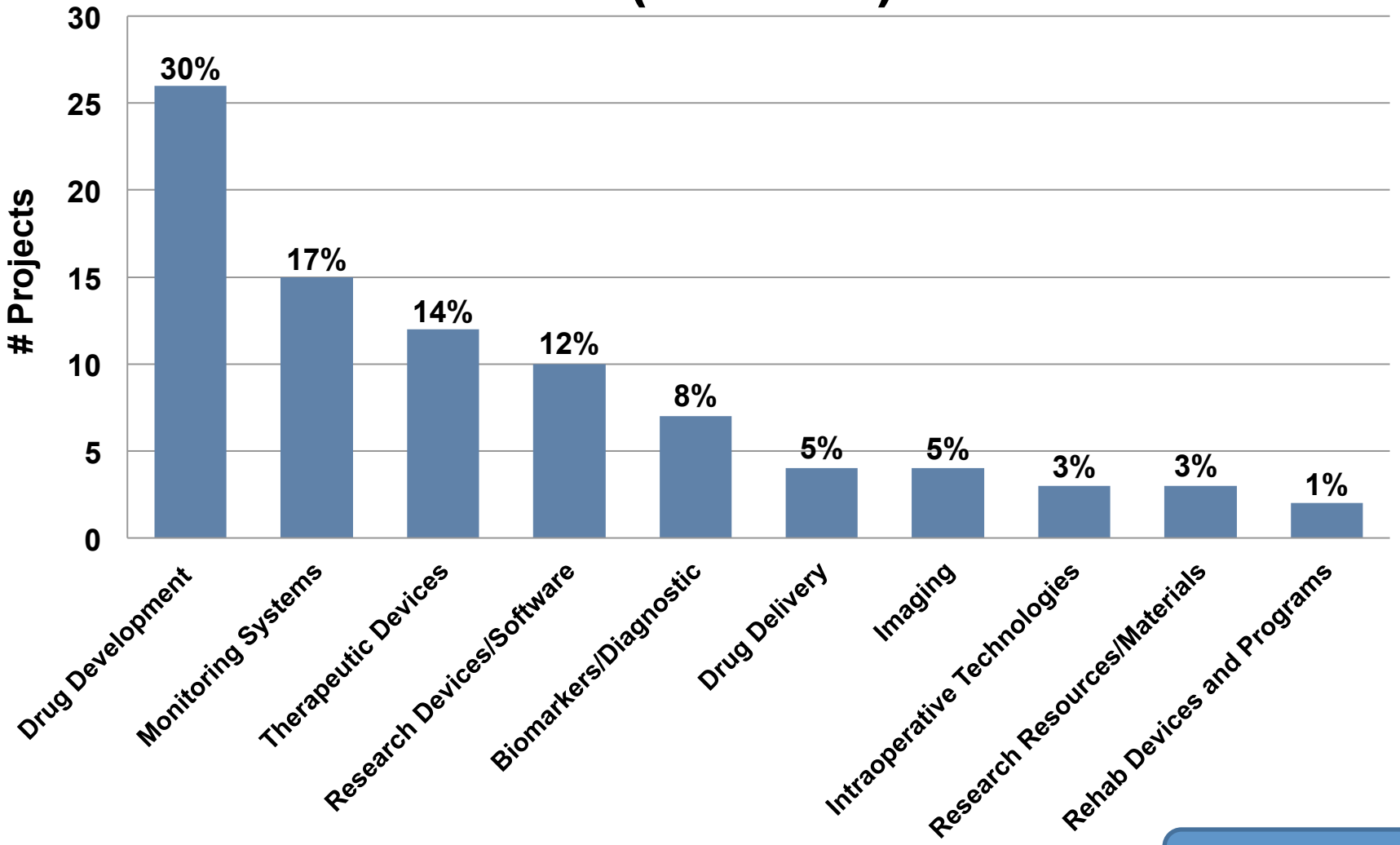
Small Businesses by Indication (FY2012)



Other:

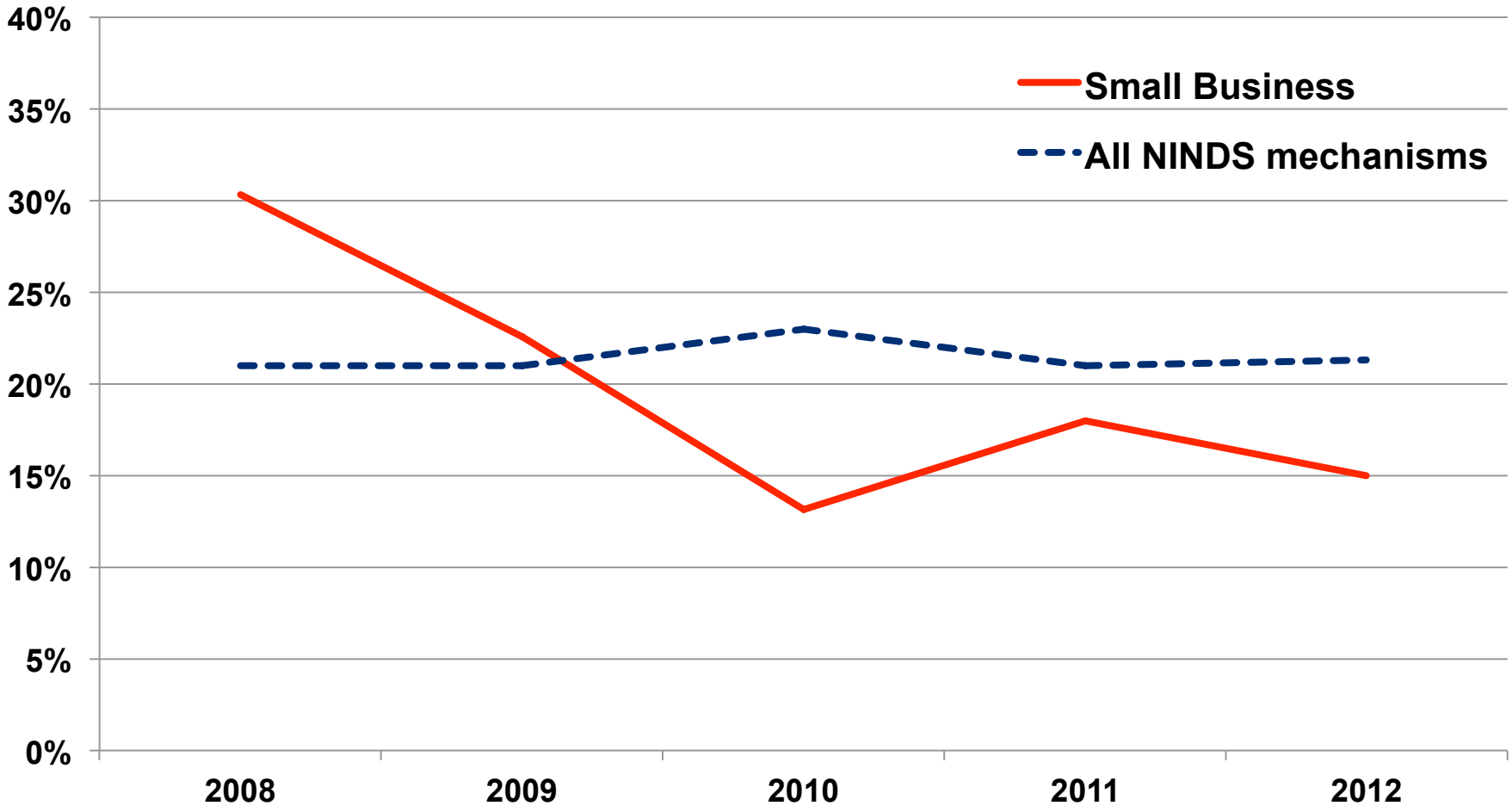
- ALS
- Aneurysm
- Ataxia-telangiectasia
- Creutzfeldt-Jakob Disease
- Diabetic Neuropathy
- Education
- Huntington's
- Metachromatic Leukodystrophy
- Meningitis
- MS
- SCI

Small Businesses by Interventional Modality (FY2012)



Devices: 49%

Small Business Success is Comparable to Overall Rate

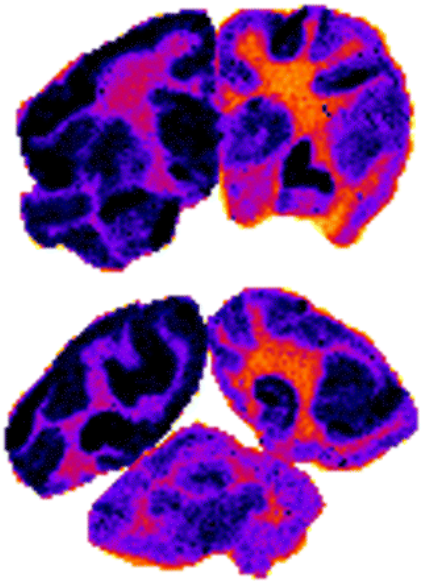


New Small Businesses Continue to Seek Funding

- NINDS supported 68 companies (1.2 grants per company)
- Of the new awards (2012):
  - 65% from companies new to NINDS
  - 22% from companies new to NIH

Drug Development Success: ArmaGen

- The idea: fuse a therapeutic protein with an antibody that can cross the BBB
- Targeted Neurotrophin Drug Development in Parkinson's Disease
- Bioengineering of a New Decoy Receptor Drug Delivery Technology
- Nov 30, 2012: $17M series A financing to support the development of the "molecular Trojan horse technology."



Film autoradiography of rhesus monkey brain removed 2 h after an intravenous administration of ^{125}I-HIR MAb-GDNF fusion protein. Coronal sections through the cerebrum (top) and hindbrain/cerebellum (bottom) are shown. Intensity increases from red-yellow to blue-violet. Drug Metab Dispos. 2009 Dec;37(12):2299-304. Epub 2009 Sep 9.

Device Success Story: FHC, Inc.

- Founded in 1970
- National Tibbetts Award 2012
- Software Guided Localization of the Subthalamic Nucleus During DBS Surgeries
- Instrument for Intracerebral Microinjections and Electrophysiology
- SBIR supported evolution from research base to device development
- Has products on the market, used by physicians and researchers
  - Array electrodes
  - Microtargeting electrode (market-leader world wide)
  - Microrecording and stimulating
  - Temperature controllers

FHC Products to Watch for in the video:

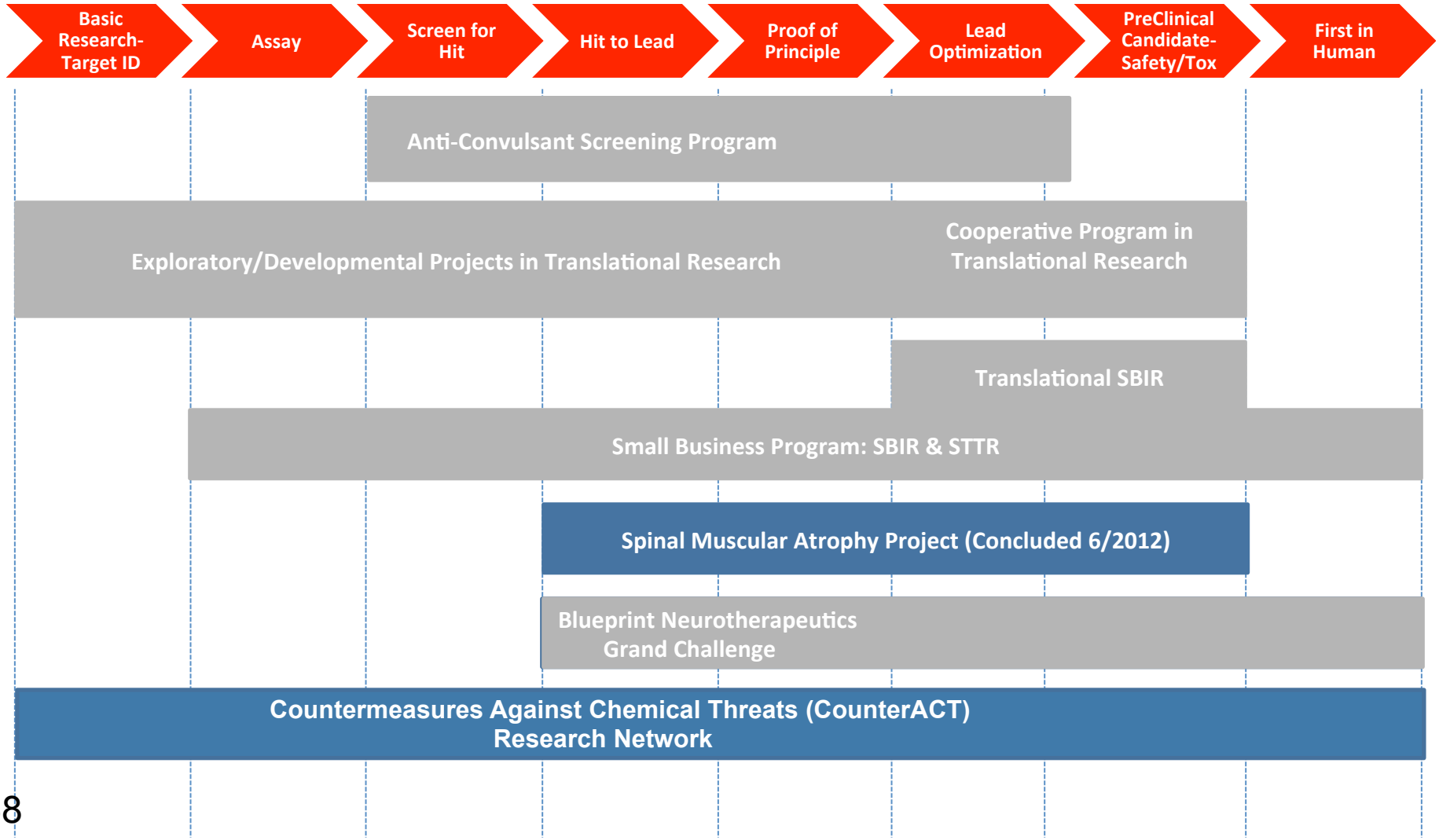
Microtargeting Drive
(positions the electrode)

DBS Platform
(patient-specific frame)

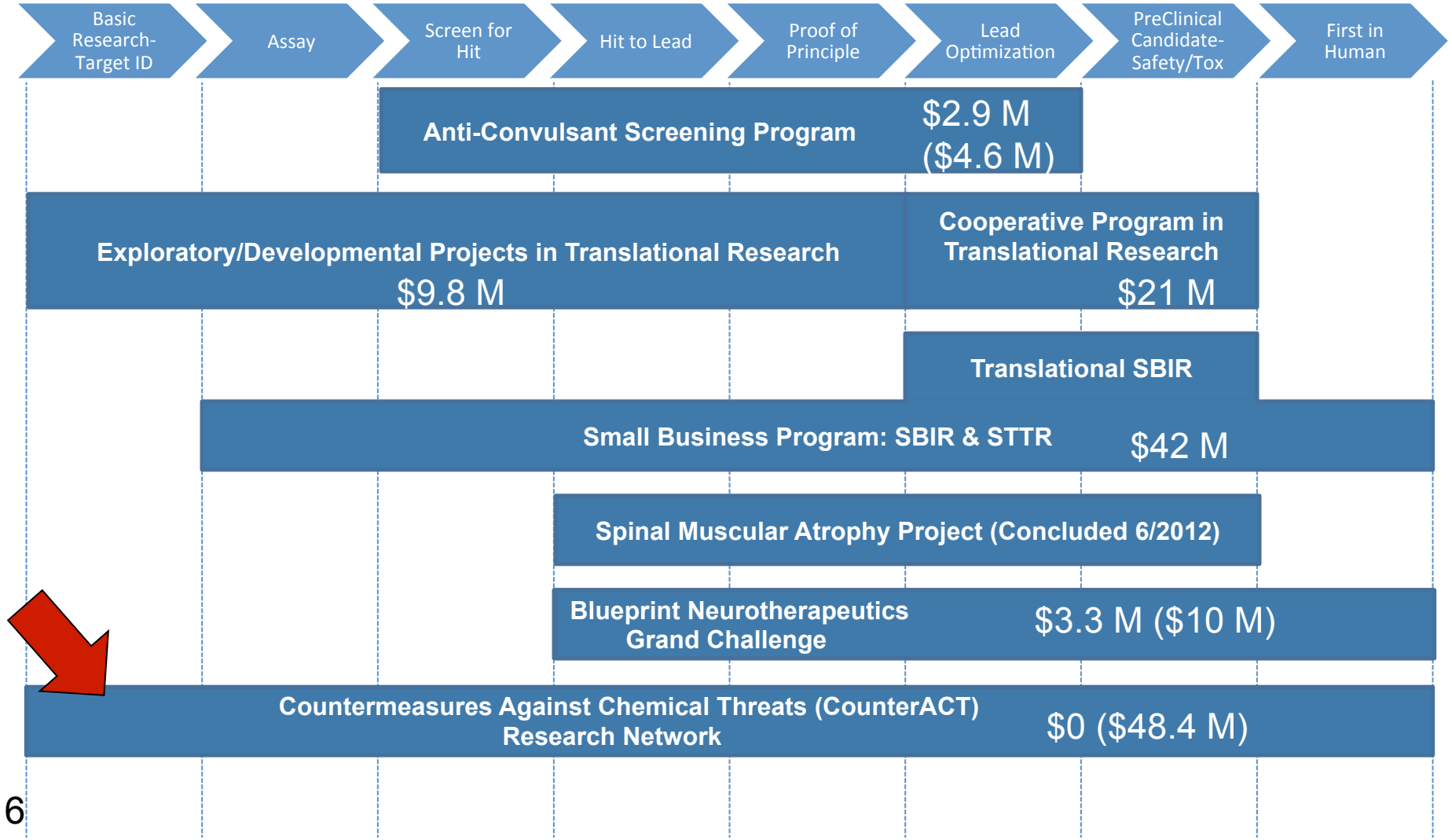
Software

DBS Electrode

OTR uses a Variety of Approaches for Translation



A Variety of Approaches to Translation



NIH CounterACT
Countermeasures Against Chemical Threats

Mission:

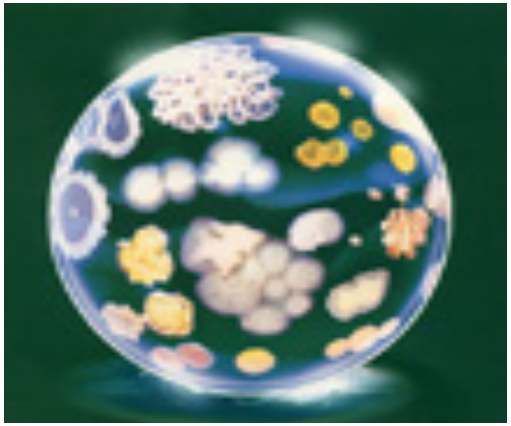
To develop FDA-approved therapeutics and diagnostic technologies that will reduce mortality and morbidity during and after chemical emergency events.

Biodefense Programs at NIH

NIAID Oversight

NIAID Management

NINDS Management



Biological

- Category A, B, C
- Bacterial, e.g. anthrax
- Viral, e.g. small pox
- Toxins, e.g. botulinum

(FY12 $1, 700 M)

Radiation/Nuclear

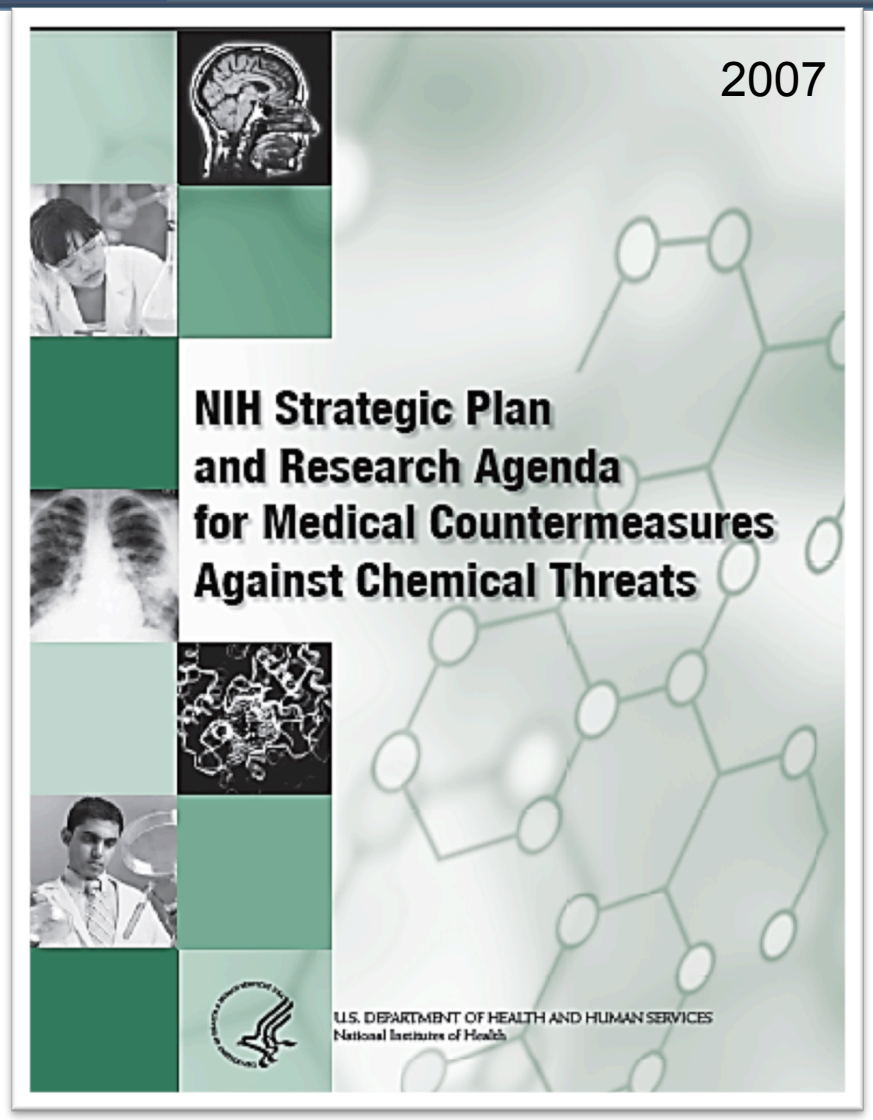
- Bomb detonation
- Radiation Dispersal
- Attack on n. reactor
- Or on spent fuels

(FY12 $47 M)

Chemical

- Industrial, cyanide
- WMDs, e.g. sarin
- Pesticides, e.g. parathion
- Toxins, e.g. picrotoxin

(FY12 $48 M)



"Treatments must be appropriate for a diverse civilian population"

"Treatments must be formulated so they can be administered easily and rapidly in a situation involving mass casualties"

"Immediate as well as long-term effects of exposure to chemicals must be understood"

Burden of Illness

Chemical Warfare

- World War I and II: *thousands of fatalities*
- Iran-Iraq War (1980-88): *thousands of fatalities*
- Current conflicts in the Middle East: *unknown*

Terrorism/Non-military malicious use

- Tokyo Subway Attacks (1995): *thousands affected; 13 fatalities*
- Jonestown mass suicide (1978): *900 fatalities*
- Tylenol and Excedrin poisonings (1980's): *few fatalities*

Industrial Accidents

- Occur Daily; *thousands* of injuries and fatalities annually
- Bhopal Union Carbide disaster (1984): *5,000 fatalities*

General Poisonings

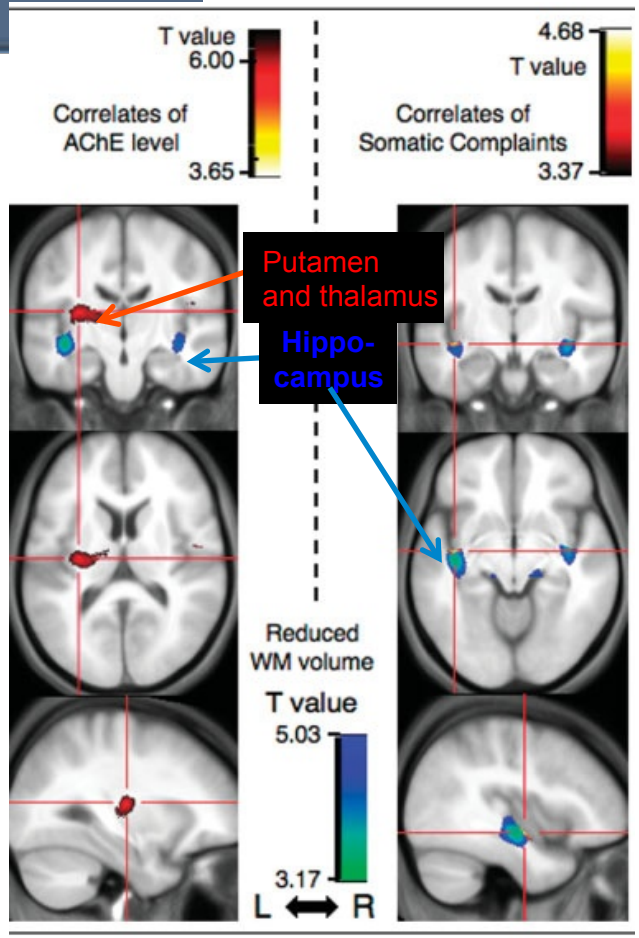
- *4.2 million* calls to Poison Control Centers in 2009 alone

National Institute of Neurological Disorders and Stroke

>1,000 victims, 12 deaths

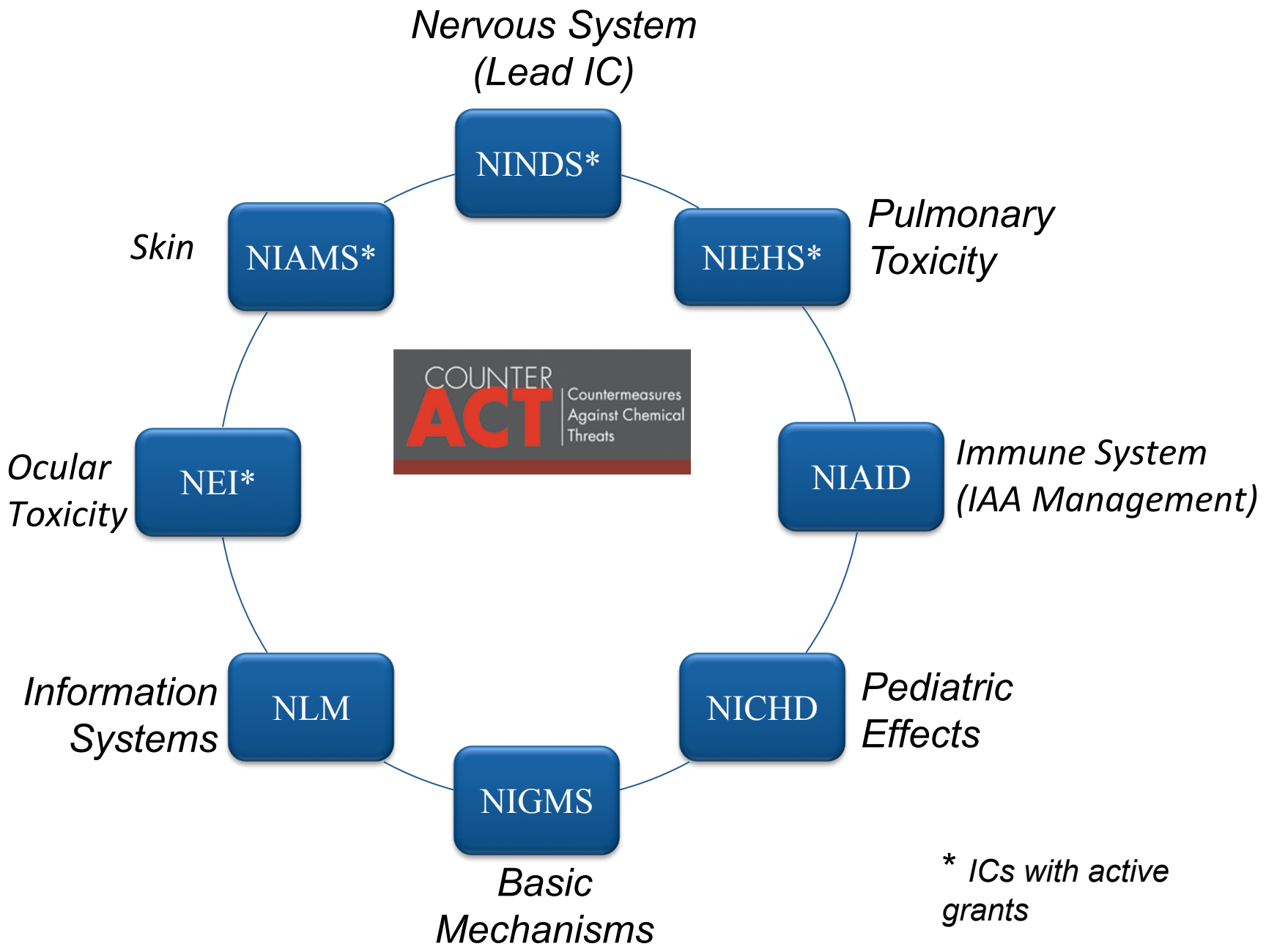
Human Brain Structural Change Related to Acute Single Exposure to Sarin

Hidenori Yamasue, MD, PhD,[1] Osamu Abe, MD, PhD,[2] Kiyoto Kasai, MD, PhD,[1] Motomu Suga, MD,[1] Akira Iwanami, MD, PhD,[3] Haruyasu Yamada, MD, PhD,[2] Mamoru Tochigi, MD,[1] Toshiyuki Ohtani, MD, PhD,[1] Mark A. Rogers, PhD,[1,4] Tsukasa Sasaki, MD, PhD,[1] Shigeki Aoki, MD, PhD,[2] Tadafumi Kato, MD, PhD,[5] and Nobumasa Kato, MD, PhD[1]

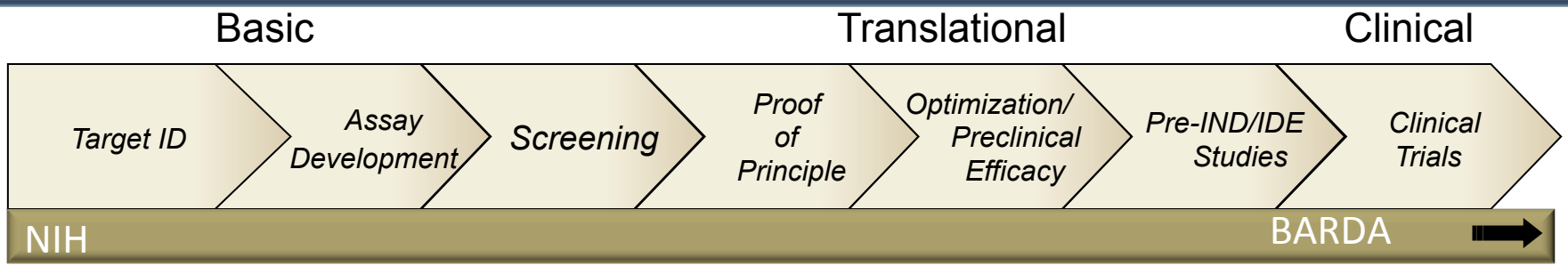


"…smaller than normal regional brain volumes in the insular cortex and neighboring white matter, as well as in the hippocampus in the victims. The reduced regional white matter volume correlated with decreased serum cholinesterase levels and with the severity of chronic somatic complaints related to interoceptive awareness [anxiety]." ($p < 0.05$) Annals of Neurology

Program Structure and Management


Nervous System
(Lead IC)
NINDS*
Skin
NIAMS*
NIEHS*
Pulmonary
Toxicity
COUNTER
ACT
Countermeasures
Against Chemical
Threats
Ocular
Toxicity
NEI*
NIAID
Immune System
(IAA Management)
Information
Systems
NLM
NICHD
Pediatric
Effects
NIGMS
Basic
Mechanisms
* ICs with active
grants

NIH National Institute of Neurological Disorders and Stroke



Centers of Excellence (U54) and Individual Projects (U01)

DoD Laboratories (IAAs)

Efficacy Research Facility

Medicinal Chemistry (proposed)

Preclinical Contract Facility

Clinical Trial Networks

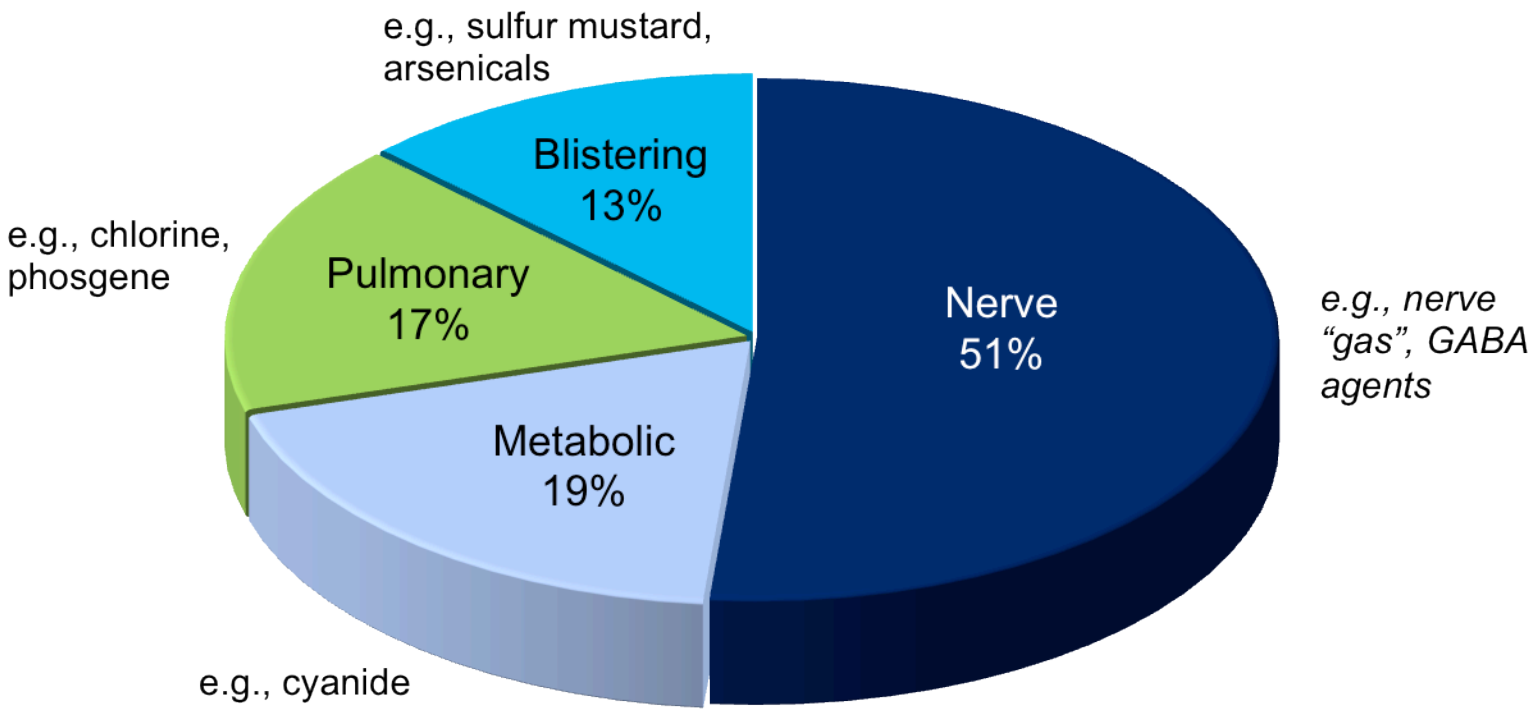
Industry Partners (SBIRs, Subcontracts to Grants)

Regulatory Affairs Consultative Bureau

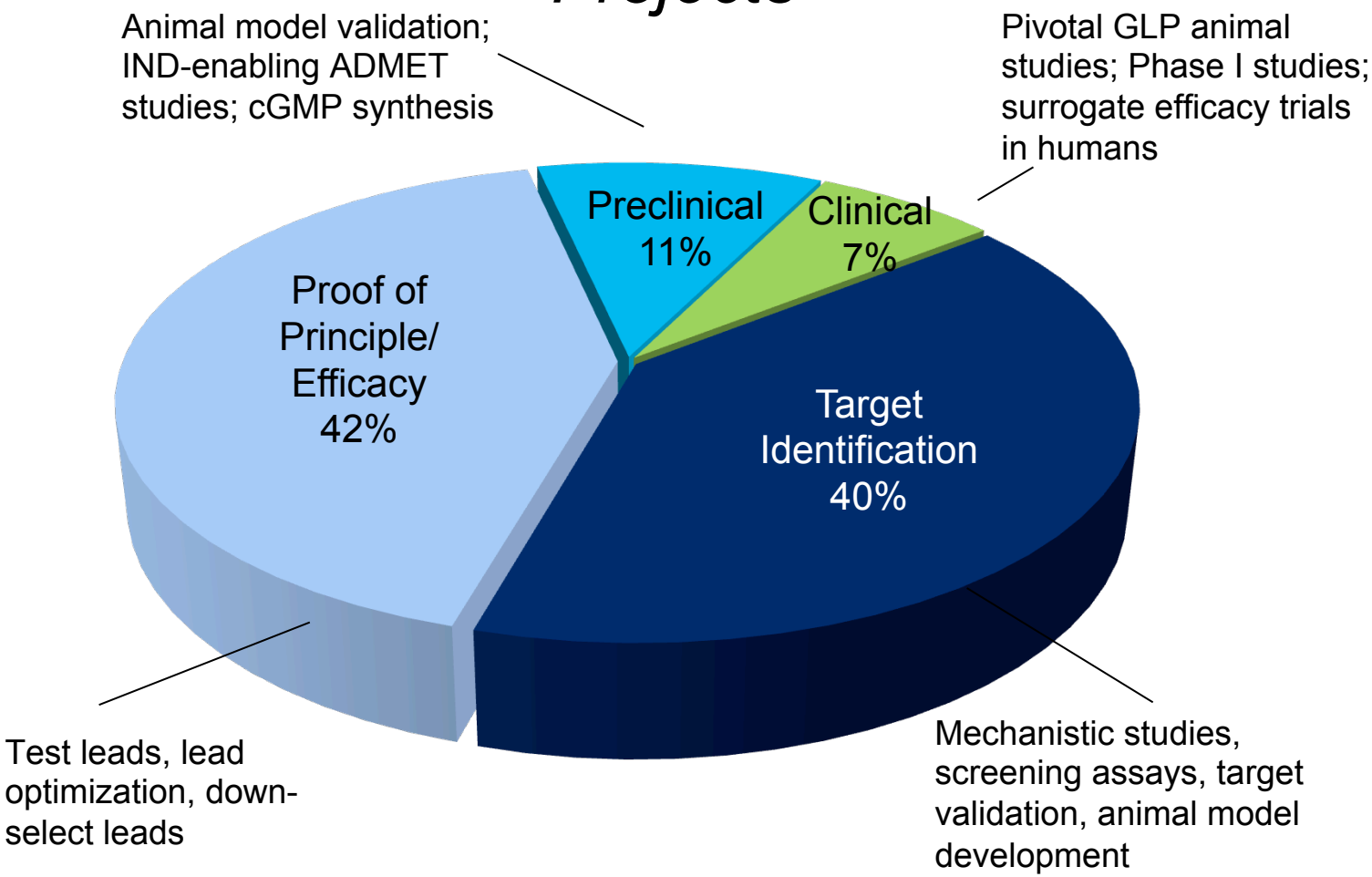
COUNTER ACT Countermeasures Against Chemical Threats

The CounterACT Portfolio

Chemical Classes



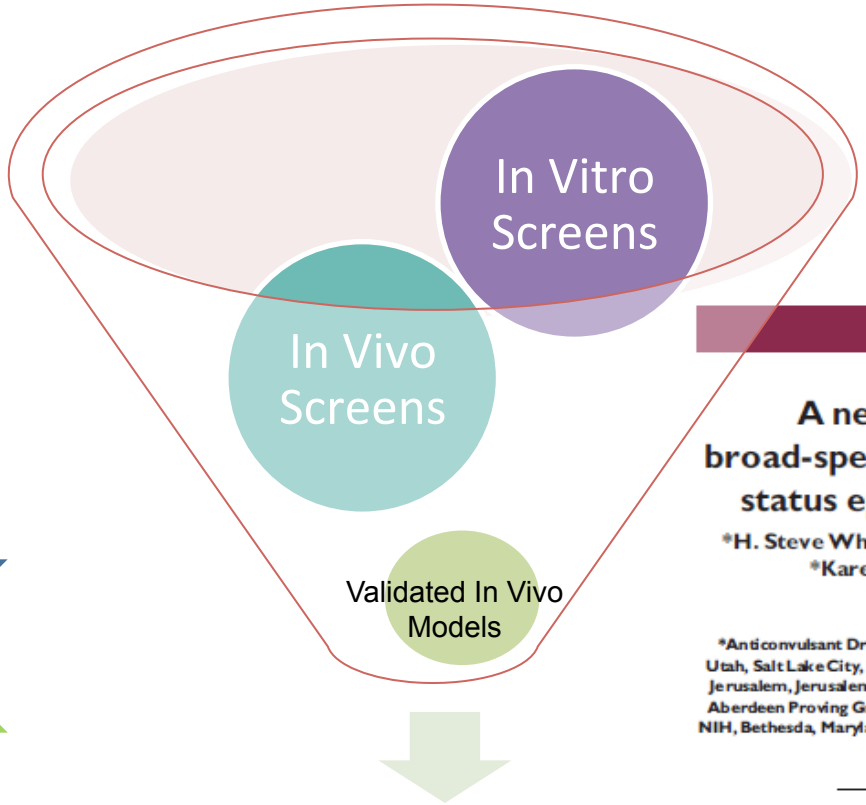
Development Stage of Projects



Key Partnerships

CounterACT and ASP Partnership

ASP



ARMY

Institute of Chemical Defense

BATTELLE

Epilepsia, 53(1):134–146, 2012
doi: 10.1111/j.1528-1167.2011.03338.x

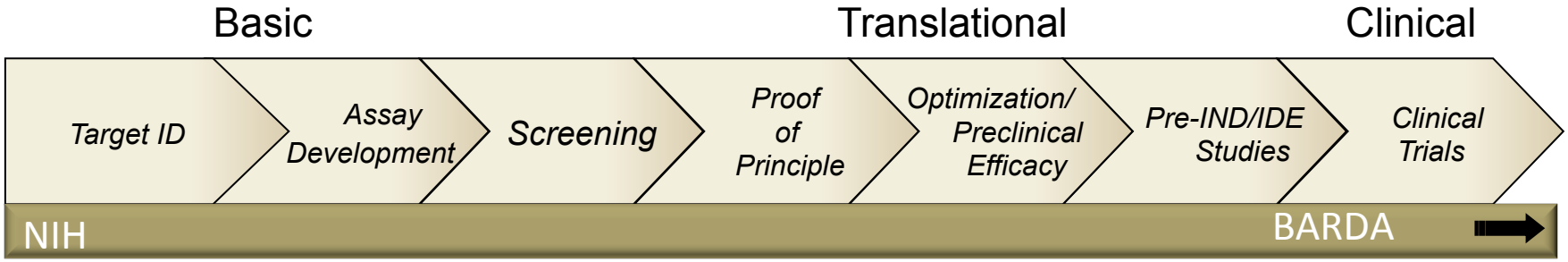
FULL-LENGTH ORIGINAL RESEARCH

A new derivative of valproic acid amide possesses a broad-spectrum antiseizure profile and unique activity against status epilepticus and organophosphate neuronal damage

*H. Steve White, *Anitha B. Alex, *Amanda Pollock, †Naama Hen, †Tawfeeq Shekh-Ahmad, *Karen S. Wilcox, ‡John H. McDonough, §James P. Stables, †Dan Kaufmann, †¶Boris Yagen, and †¶Meir Bialer

*Anticonvulsant Drug Development Program, Department of Pharmacology and Toxicology, College of Pharmacy, University of Utah, Salt Lake City, Utah, U.S.A.; †Faculty of Medicine, Institute for Drug Research, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel; ‡Pharmacology Branch, Research Division, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland, U.S.A.; §Anticonvulsant Screening Program (ASP), Office of Translational Research, NINDS, NIH, Bethesda, Maryland, U.S.A.; and ¶Affiliated with the David R. Bloom Centre for Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel

Products in the Pipeline



Over 30+ "hits" and/or targets identified

Neuregulin
Brovana*
Rolipram
Sulfanegen
Galantamine*
LY293558
AEOL 10150 (M)
Doxycycline*

Cobinamide (M)

Midazolam*

Drug indication:
Black = Vesicants
Red = Nerve Agents
Blue = Pulmonary Agents
Green = Cyanide
(M) = *multiple indications*

* *Denotes FDA-approved compound for another indication*

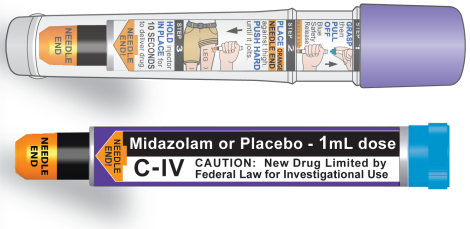
RAMPART: A Partnering Success Story: NIH, DHHS, DoD, Pfizer, U. Michigan

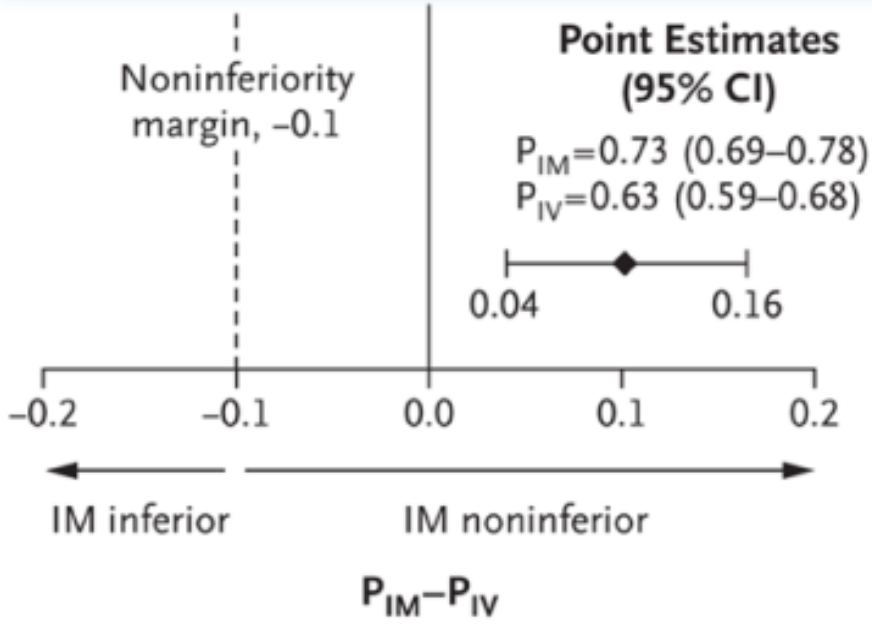
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 16, 2012 VOL. 366 NO. 7

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*





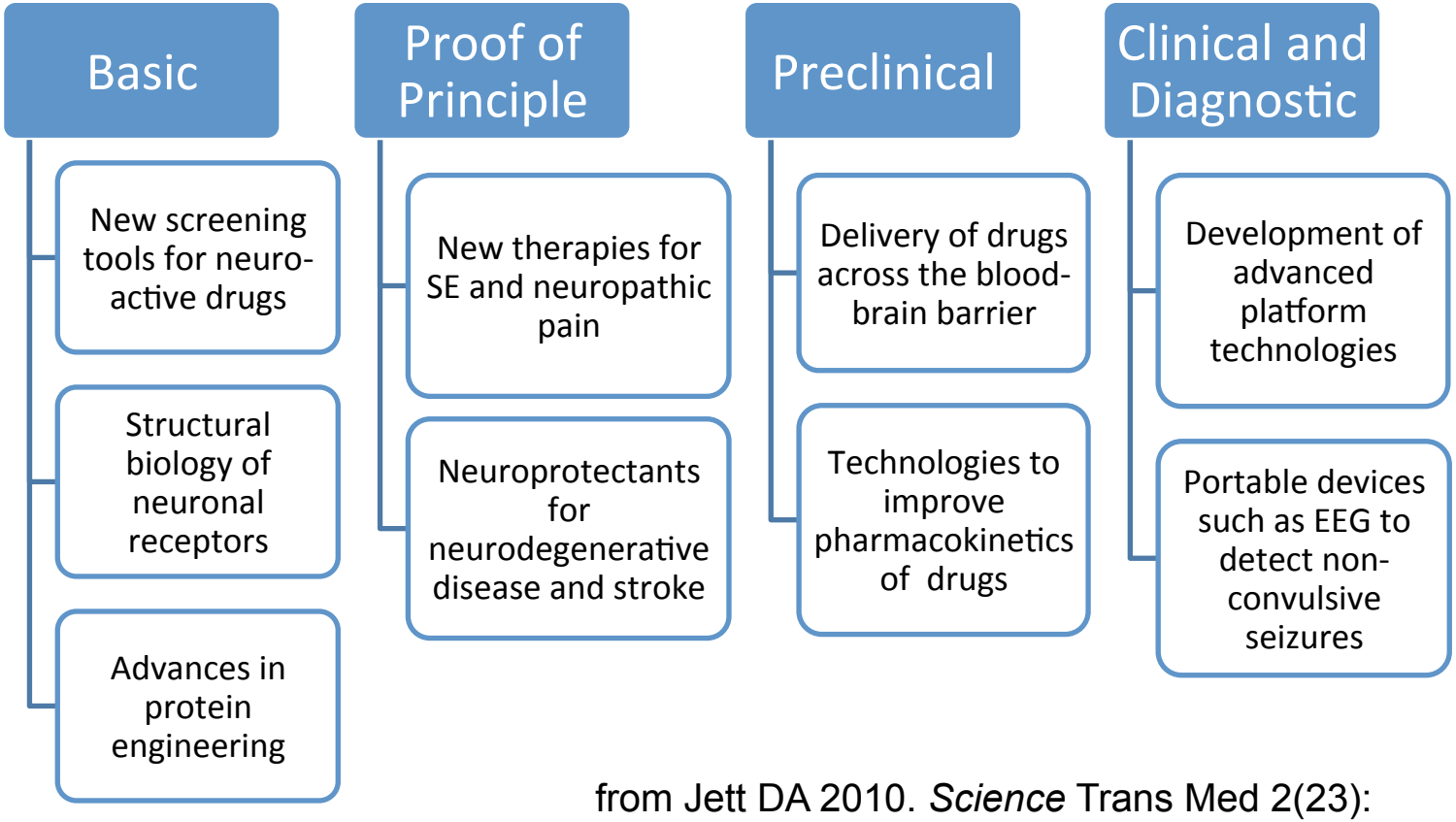
Hypothesis: IM midazolam is as effective as IV lorazepam at stopping convulsions prior to ED arrival.

Method: Double blinded, Double Dummy; 4,314 paramedics, 79 hospitals. 1,023 enrolled.

Conclusion: Intramuscular midazolam is the optimal initial prehospital treatment for status epilepticus by paramedics

Accompanying editorial: "…the findings in this study should lead to a systematic change in the way patients in status epilepticus are treated en route to the hospital." −*Lawrence Hirsch*

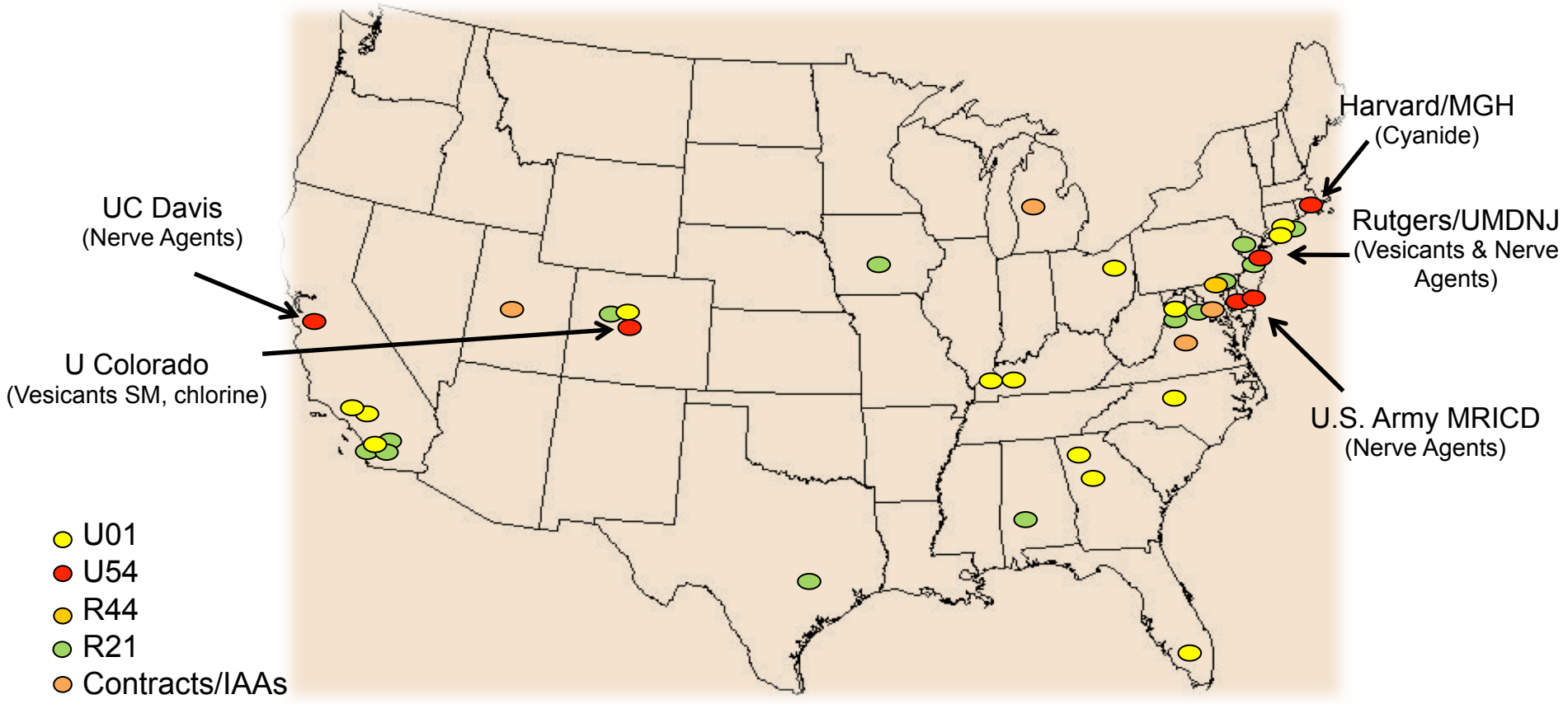
And CounterACT research can have broad implications



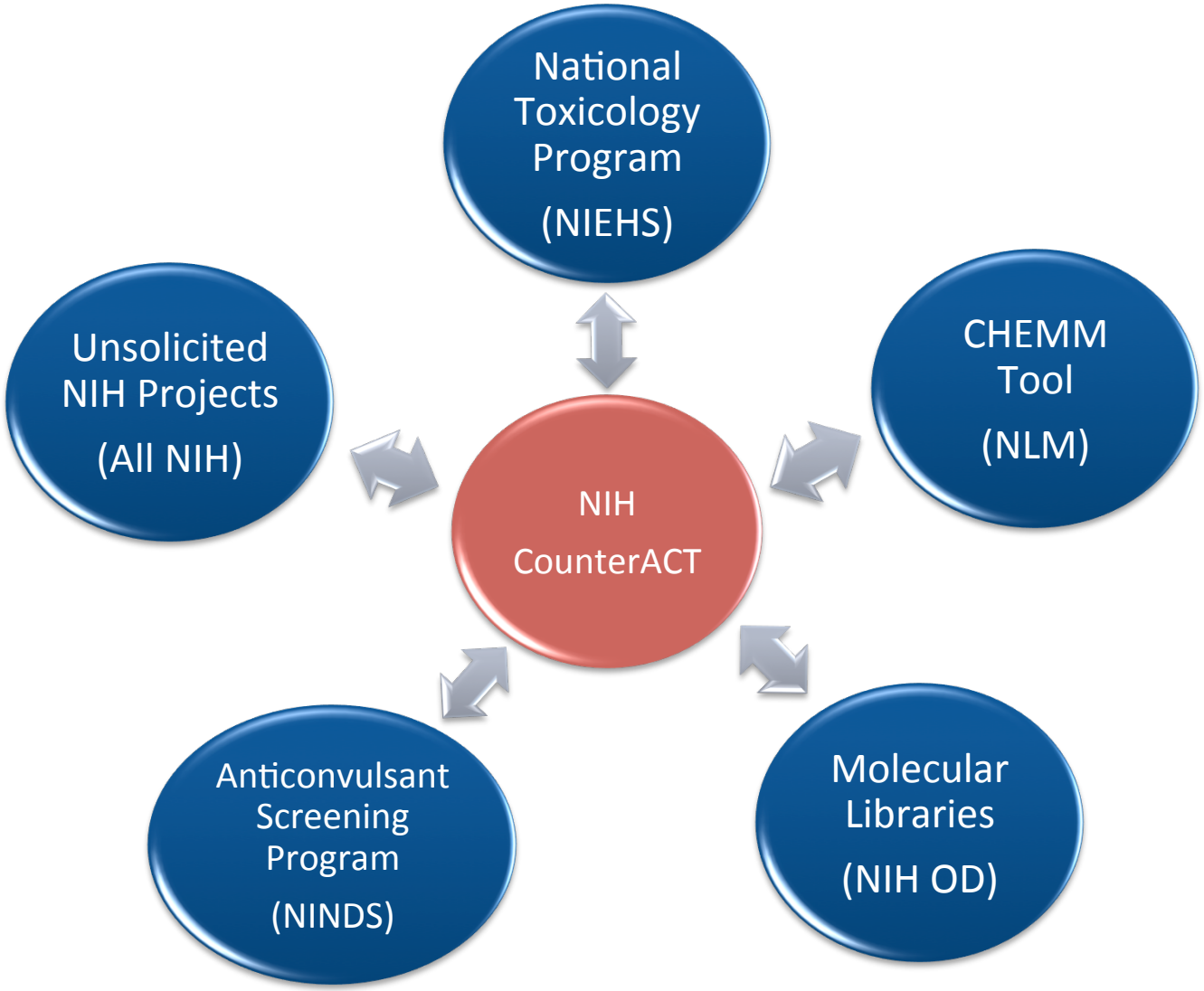
from Jett DA 2010. *Science* Trans Med 2(23): 23ps12

COUNTER ACT | Countermeasures Against Chemical Threats

Research Network



Other Partnerships



OTR Guiding Principles

- Need to get therapeutics to humans (not bench to bookshelf)
  - Cooperative program now allows for Phase 0
- Needs to be done in collaboration with others
  - BPN utilizes resources across ICs and relies on outside experts
  - CounterACT works with multiple agencies
- Have to adapt efforts to ever-changing landscape
  - SBIR/STTR is providing “seed money” where investors won’t and is shortening the time to award
  - We are engaging in outlicensing efforts (SMA)

Questions?

rajesh.ranganathan@nih.gov